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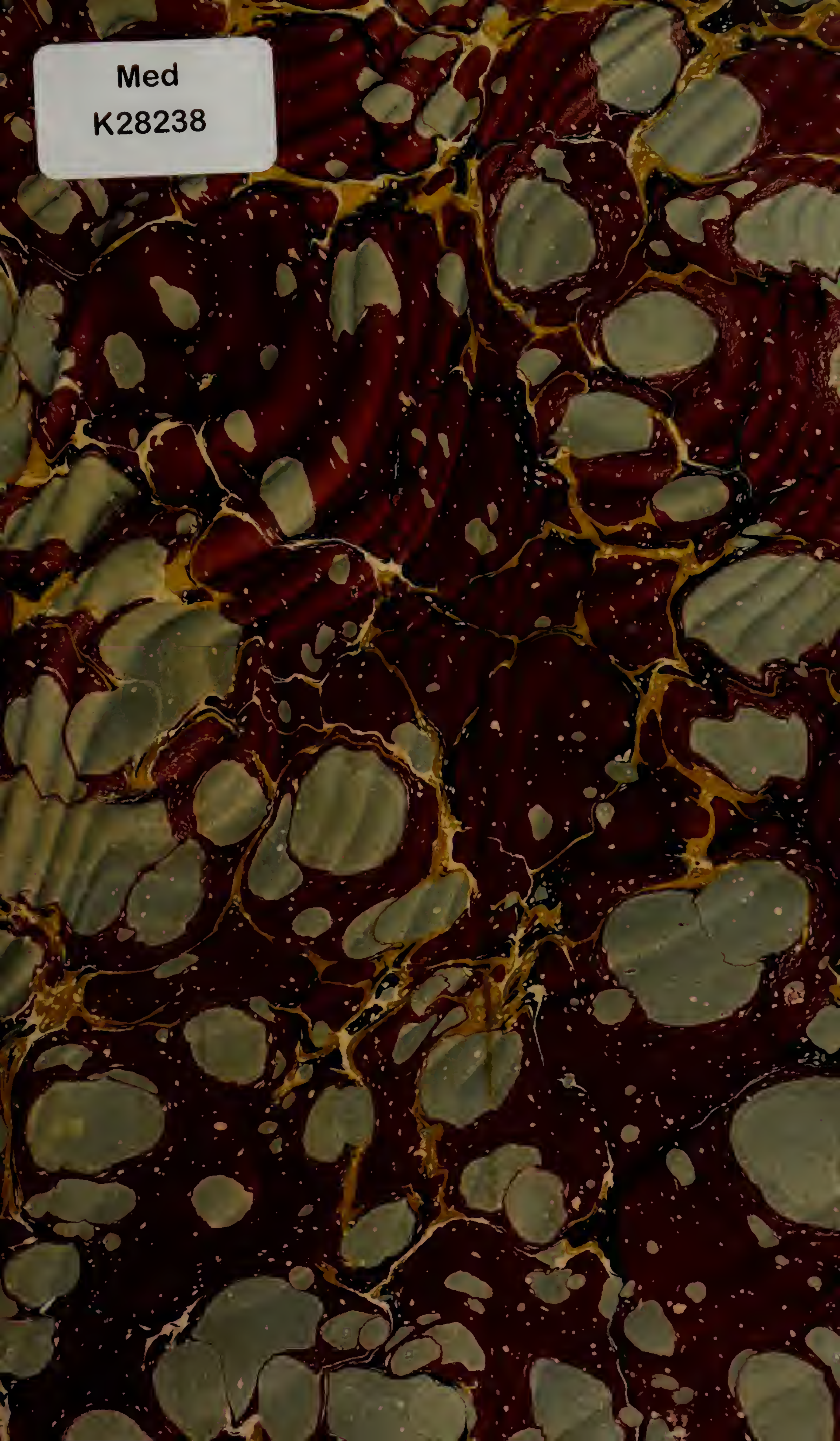

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THE PATHOLOGY AND ETIOLOGY
OF
INFECTIOUS DISEASES

BY

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INTRODUCTION

Few branches of medical science can be said to have received, within the last twenty-five years, greater attention, and to have developed more largely within a comparatively short period, than the knowledge of the nature of infectious diseases. Not only have many disorders, belonging to this class and for a long time suspected as belonging to this group, become well understood in their nature, their mode of origin and spread, but others, not previously suspected to be communicable diseases at all, have been shown to appertain to this class. To quote for each of these one instance: typhoid fever, though for a long time assumed to be a communicable disorder spreading from the sick to the healthy by the evacuations, had not, prior to the researches of Budd, Snow, Simon, Buchanan and others, been proved to be of this character, and though some authorities, like Murchison, pleaded for the possibility of a spontaneous origin, the weight of evidence was in favour of its being a specific disease, which, like all specific diseases, can only arise from a previous specific disorder of the same kind. By the researches of more modern investigators, notably Buchanan, Ballard, and Thorne Thorne, its mode of spread has become well understood, and by their investigations its nature—viz. that of a specific communicable disease—been definitely settled. As examples of diseases not previously suspected to belong to this group but now known to be so, we may quote tetanus, and epidemic or croupous pneumonia. Of both these diseases recent research has shown that they are of an infectious character, that in both there exists a specific virus which, finding entrance into a healthy individual, is capable of setting up the disorder. These examples we could easily multiply. Nay more, we could show, on the one hand, that as regards a number of disorders for whose specific nature there existed until quite recently very slender evidence, there are now definite and exact experimental grounds for asserting their specific nature, e.g. anthrax, tuberculosis, septicæmia, and erysipelas; on the other hand, by ascertaining the exact nature of some of these disorders, others formerly not distinguished from them have been shown to have a separate existence and to be different from them in their pathology, symptoms, course, and causation. Thus, for instance, malignant anthrax has been shown to be a perfectly separate disorder from symptomatic anthrax; woolsorters' disease (malignant pustule) to be a separate disease from some forms of ragsorters' disease; tuberculosis to be different from other chronic lung diseases, to which it bears a distant pathological semblance.

These results have been achieved by the isolation and study of the essence of these diseases—the *contagium*, which was shown to be a living microphyte,[1] *contagium vivum*, differing as regards morphology and biology in the different diseases to which it gives rise. It is no doubt an interesting study to trace the history and the development of the theory of the *contagium vivum*; but at the present day such a study is chiefly of an historical interest, and not an integral part of the present work. It is interesting to go back to the time when the basis of a discussion as to whether infectious diseases can arise *de novo* was evidence such as the existence of epidemics arising from a case imported from outside (small-pox, the plague, cholera, &c.); or evidence that the isolation of the patient, and destruction of matter derived from such a patient, puts a stop to, or prevents the spread of that disorder; or when the similarity of the specific nature and spread of infectious diseases to the specific nature of fermentations, such as those specially studied and revealed by the earlier labours of M. Pasteur, was insisted on. At present the evidence that infectious diseases owe their origin to specific well-characterised micro-organisms, which, having entered, in however small a number, a susceptible human or animal body, multiply therein, and set up the whole chain of symptoms characterising the particular disease; and further, that the diseased tissues of such an infected individual harbour the specific microbes, so that a minute particle of such tissue is again capable of starting the disorder in a new body;—all this is no longer a matter of assumption and indirect evidence, but one of exact science. Just as a chemist is enabled to detect and to demonstrate with tolerable exactness the existence in special cases of a chemical poison—e.g. arsenic, phosphorus, strychnine, &c.—the material that has caused disease and death, so nowadays can the pathologist by microscopical, cultural, and animal experiments demonstrate the specific *materies morbi*; more than that, in cases where the physician, or surgeon and sanitarian, is unable by the clinical and other aspects of a case to give an opinion, the pathologist can by his methods state with exactness the nature of the disease in question. In illustration of this we may mention the case of tuberculosis, of anthrax, of cholera, and of hydrophobia. Numerous cases occur in the human subject where from a clinical point of view the physician does not feel justified in pronouncing whether or not the case is one of tuberculosis; the pathologist, by demonstrating the presence or absence of the tubercle bacilli, is enabled to settle the point without difficulty. The same holds good in certain surgical cases, where the diagnosis of tuberculosis of the skin or bones is only possible after the demonstration of the tubercle bacilli. In certain diseases affecting sheep and cattle, and wool and hide sorters, the exact and reliable diagnosis of malignant anthrax is furnished by the demonstration of the bacillus anthracis by the microscope, by culture, and by experiment on animals. In suspected cases of cholera, when the clinical aspect is not sufficiently characteristic, the demonstration of the choleraic comma bacilli in the evacuations, or in the contents of the intestines, furnishes an important piece of evidence. In cases of suspected rabies, the experimental method discovered by M. Pasteur—viz. that the spinal marrow of such an animal inoculated under the dura mater of a rabbit produces hydrophobia—furnishes positive proof. The differential diagnosis between tuberculosis and actinomycosis in cattle, possible by the microscopic test, furnishes another not less important illustration. The study of micro-organisms connected with specific diseases—i.e. the *contagia*, their nature, habits, and mode of growth, outside and within an infected individual, the manner in which they leave and in which they enter the human and animal organism, the nature of the changes which they induce in the material in which they grow and multiply, be that material the human or animal organism, or organic matter outside these—all this is now well understood.

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[1] *μικρός*, small, *φυτόν*, plant.

The micro-organisms or microbes[1] that interest us belong to three distinct groups: (1) bacteria, (2) fungi, (3) monadinæ. The first are those which as regards infectious diseases hold the most prominent place, owing to their general and very wide distribution, and because most of the infectious disorders hitherto analysed owe their origin to one or another species of these microphytes; the second or fungi have, so far as research has hitherto gone, a more limited distribution as disease-producers; and the third group, or monadinæ and allied organisms, belonging to the animal kingdom, are at present only imperfectly investigated, although, as will be shown, they produce some well-marked disorders in man and animals.

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[1] Microbe (*μικρός*, small, *βίος*, life) is the term also generally applied to these microscopic organisms.

SECTION A.

CHAPTER I

CHARACTERS OF BACTERIA

BACTERIA are microscopic organisms which contain no chlorophyll, which possess an investment of cellulose, and are therefore considered to belong to the vegetable kingdom, which multiply by simple division or fission, and are therefore called, after Naegeli, Schizomycetes (σχίζω, divide, and μύκης, fungus). Though they are considered as single-celled plants, their action is not quite in harmony with that generally attributed to plants, since, speaking in a general way, they do not possess in any conspicuous degree, like vegetable cells, the power of building up complex organic substances from simple inorganic material; but, on the contrary, on the plan of animal cells, they have in an eminent degree the character of destroying or breaking down higher or complex organic molecules into those of simpler combinations. This is true in a general way, although, just as is the case with animal cells, exceptions are not wanting, i.e. instances when by synthetic processes the reverse takes place.

GENERAL MORPHOLOGY

We will first consider the general morphological characters of bacteria. Bacteria are single cells of extremely minute size, 0·1 to 1μ[1] or more, consisting of a protoplasmic body—mycoprotein of Nencki, and an investing sheath of cellulose. The protoplasm while active and living is homogeneous, when dead often appears granular; it has great affinity for neutral and basic aniline dyes, and in this respect compares with the substance of nuclei in vegetable and animal cells. There is no evidence of the presence in their protoplasm of any differentiation comparable to the nucleus in the animal or vegetable cell, although in some individual cases such a structure has been mentioned, but this, owing to the methods of complex staining used for its demonstration, is not free from objection; in the fresh state, and after the usual methods of staining, no differentiation of a nucleus can be recognised in the active and living cells constituting the elements of any bacterial species. The protoplasm does, however, show in certain conditions and in certain species differentiation of denser and less dense parts, causing a segregation of the protoplasm into granules or particles; this occurs in conditions generally taken as indicating degeneration, but in several instances, to be mentioned later, is a character belonging to the life of the bacteria. Similarly, the appearance of fluid droplets in the protoplasm—vacuoles—can be noticed in certain conditions. In some organisms granules of a special chemical nature have been noticed in the protoplasm (Cohn). The process of vacuolation is constantly noticed in conditions of fairly rapid multiplication; the bacterial element elongates more or less, generally in the middle of its protoplasm a vacuole appears, and hereby the protoplasm segregates into two polar masses. Such forms are very numerously met with in all species of bacilli, and under the most varied conditions of growth and multiplication; often these vacuoles have been, and still are, occasionally mistaken for spores (*see* below). The cellulose sheath invests closely the protoplasm; when the cells degenerate the protoplasm breaks down and disappears, and the sheath remains empty; during this process the sheath as a whole swells up into a jelly, faintly granular, and gradually loses altogether its outlines. In many species of bacteria during rapid multiplication the sheath gives rise to a gelatinous secretion surrounding the individuals, in fact forming a kind of general matrix—hyaline, viscous, and more or less faintly granular—for the new brood, and by this matrix a larger or smaller number of the new individuals remain aggregated together: it is not quite clear whether this matrix is derived from a gelatinous metamorphosis of the old sheaths, or whether it is a secretion or new formation by the new elements. When, in an individual, the protoplasm divides into two masses, each of the new offsprings forms its own investment, so that the old sheath, swelling up into a gelatinous mass, persists as a sort of binding matrix; in all those species in which, after continued division, new elements remain aggregated together as groups (zooglæa, staphylococcus), the gelatinous matrix has this origin (Cohn). In other cases the bacteria become invested outside the sheath by a gelatinous secretion, which as a narrower or broader hyaline-looking zone invests the elements like a capsule, e.g. ascococcus Billrothi, bacillus cyanogenus, bacillus pneumoniæ of Friedländer, and other capsulated cocci and bacilli of the same tribe. In these instances of 'capsulated' bacteria the capsules are probably special secretions and not the old swollen-up sheaths, since these capsules are wanting under certain different conditions of soil, while they are present and well marked in other conditions, the rapidity of multiplication having no influence whatever on the presence or absence of these capsules. These hyaline capsules around the sheath must not be confounded with the swollen-up gelatinous sheath of bacteria in certain phases of their life, notably in the degenerative phases.

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[1] 1 μ = one micromillimetre = one twenty-five thousandth of an inch.

The affinity of the protoplasm towards certain aniline dyes is greater than that of the sheath, and that of the latter greater than of the matrix and capsules above mentioned, so that on staining with an aniline dye, the protoplasm takes up the dye quicker and more intensely than the sheath or the matrix; and on withdrawing the dye, by washing in alcohol, or water, acids, or alkalies or other special methods (*see* below), the protoplasm retains it longest, the capsules and matrix least. For this reason it will be found that by either of these ways it is possible to bring out these three different structures as different tints of the same dye, and further, that, owing to the rapidity with which the matrix and capsules can be deprived of the dye, a second dye can be applied, to be taken up by them while the protoplasm and sheath have still retained the first dye. By these means various double, and even treble, stainings can be effected by successive applications of different dyes. Acids and alkalies, chloroform, and alcohol, though affecting the fresh protoplasm, have no visible effect on the sheath, and bacteria acted upon by these reagents remain, therefore, unaltered both as to shape and aspect; and these chemical reactions are often resorted to for the sake of differentiating bacteria—notably the spherical species—from similar forms of organic matter not of bacterial nature. This is particularly important in the examination of animal tissues in the fresh state, in which tissue granules and rod-like forms, fat granules, &c., may easily give semblance to the presence of bacteria, but the test of acids and alkalies soon brings clearness into the matter. Other tests to be presently described, such as staining and cultivation, are of importance, and add certainty to the diagnosis.

SIZE OF BACTERIA

The different species of bacteria differ one from another very considerably in size. Although all are of microscopical size, yet, comparing the different families and the different species in one family, sufficient differences will be detected to enable us to consider them as characteristic. The smallest bacteria are some of those species which, owing to their spherical form, are called cocci or micrococci.[1] But also amongst the micrococci some are of considerable diameter, 1 μ or even more; in the majority the individuals are considerably less, 0·5, 0·4, and even as small as 0·1 μ. But, as will be presently mentioned of other species, so also amongst the cocci of the same species, there occur the greatest differences in size under various conditions and in the various phases of growth. In an active state of growth, differences amounting to two and three and more times in size are noticed amongst the individuals of the same species in almost all media, sometimes less in fluid than in solid media; for though the great majority of the individuals have the same size, there are always some that are much larger. The writer has specimens of various species of micrococci, notably those capable of forming chains or chaplets when growing in fluid media (streptococci), in which some of the cocci are several times the diameter of the smallest individuals (*see* fig. 1). These large cocci can be shown to divide into medium-sized cocci, and these again into the small normal individuals.

Those forms of bacteria which, owing to their being more or less rod-shaped, are known by the name of bacilli show a diameter greater in length than in thickness. And in the size of both the thickness and length, different species vary very considerably. But it is chiefly the diameter in thickness which is for diagnostic purposes of greater importance than that in length. It must be understood that where in a given species, growing in a particular medium, the great majority of the individuals possess a certain length, this will be taken as the typical length, and is quite sufficient to serve for diagnostic purposes; but in all species of bacilli, according to the phase of growth of the individuals, the length of the rods is subject to very great variations. In characterising the length of these individuals, it is therefore necessary to give the length of the shortest and the longest individuals. But whatever the length of the different individuals, their thickness is almost uniform, and therefore this would be of greater importance than the length. As a matter of fact, in not a few species of bacteria, with which we shall become acquainted in the course of this work, the individuals often vary between slight ovals of 0·5 μ in length, and long cylinders of 5 μ or more, and it would therefore not be quite correct to say that the average length of the cylindrical cells is about 3 to 4 μ, though there may be in a particular species numerous individuals of that length; but notwithstanding these gross differences in the length of the cells, the thickness is uniform, though a few noteworthy exceptions are also here noticeable, as will be mentioned later on.

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[1] The name 'micrococci' was first applied by Hallier to the granules contained in some of his 'spores,' which granules becoming free after bursting of the 'spores' germinate into various forms of microphytes. Κόκκος means a kernel.

Another important point, apart from the variations due to phase of growth, is the influence on size of the medium in which the bacteria are growing. This is in many instances considerable. One of the best cases is that of the bacillus anthracis, though many other species (micrococci and bacilli) behave in a similar manner. Bacilli of anthrax taken from the blood of an animal dead from virulent anthrax are a little more than half the thickness of the bacilli grown in neutral broth or neutral gelatine; the majority of the rods of the former are in suitably prepared specimens made up of short, almost cubical cells, while of the latter the majority of the rods are distinctly cylindrical. But also the bacilli of anthrax derived from different species of animals dead of anthrax show differences in thickness and length. The same can be said of other bacilli (bacillus of typhoid fever, of swine fever, of tubercle, cholera, and others), both as regards length and thickness when growing in different media.

From all these considerations it follows that by naming a certain size as characteristic of the individuals of a species it is necessary to name also the source from, or the medium in which, they have been growing, and the phase of growth or length of time they have been growing, and, further, in the case of bacilli, to give the length of the shortest as well as the longest single individuals, or when the great majority are of a uniform size to state this as the typical length.

Shape of Bacteria

The first scientific classification of bacteria based on difference in shape was given by F. Cohn, and has been and still is, regarded as the most practical one, although within recent years it has undergone some not unimportant modifications. Cohn divided bacteria according to shape into: (*a*) spherical or micrococci; (*b*) oval or bacterium proper, length only twice the thickness; (*c*) cylindrical or bacilli, length more than twice the thickness; (*d*) curved or vibrio, and (*e*) spiral or spirilla, to which may be added the folded and long spirals or spirochetæ. Recent research has shown that the second division—i.e. the oval species of bacterium proper—cannot stand as a separate species or rather group of species, since more accurate observation has shown that also amongst these some of the individuals attain the cylindrical shape. This group is therefore merged into the bacilli. Likewise, it has been shown that group (*d*) cannot be separated from group (*e*), since the individuals of the species of group (*d*) in continued growth attain the shape of spirals, and *vice versâ*, that some of the spirillar forms are made up of individuals comparable to those of group (*d*). And lastly, the spirochetæ cannot stand as a separate group and must be merged with those of the spirilla. So that at present, according to shape, only three groups can be correctly distinguished, viz. (1) cocci; (2) bacilli; and (3) spirilla; the first comprises those species in which no matter what the phase or the medium is, the individuals are spherical or nearly spherical; to the second group belong all those species in which the individuals may attain the rod or cylindrical shape; and in the third the individuals are curved and may form spirals.

1. *The Cocci.*—A species in which the individuals are never cylindrical or rod-shaped cells, but are always more or less spherical, is called a micrococcus. But there are considerable differences amongst these and also amongst the individuals of the same species; for in almost all these species there are phases of growth, in which the majority of individuals are not exactly spherical, but are either crescentic or dumb-bell-shaped—diplococci.[1]

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[1] διπλοῦς, double.

Both these represent a phase in the division of the individuals; and here again the daughter cells may be in immediate contact or may be already well separated one from another, according to whether they are in the act of dividing or already divided; in the latter case, as much matrix will be found separating the new offsprings as in those that have completely divided: in this last case the individuals have the same spherical shape. In fig. 2, numerous dumb-bell forms are shown, in which the cocci are spherical; in fig. 1, dumb-bells are seen in which the cocci are crescentic; and in fig. 5, single cocci are shown, all of uniform spherical form.

Careful examination has proved that some species which in former years were considered as belonging to the group of micrococci are really bacilli, since under certain conditions of growth and, in certain phases, there are oval and even cylindrical individuals to be found amongst them, e.g. the pink organism, formerly spoken of as *Micrococcus prodigiosus*, has been shown to be really a bacillus; the organism, held by Friedländer and others to be one of the organism of croupous pneumonia, and called the pneumococcus, is really a bacillus, called now the bacillus of Friedländer, and many other species which at first sight appear in certain preparations to be cocci, and cocci only, but under other conditions of growth are shown to be bacilli; e.g. the organism which is shown in fig. 8 and which is the organism of grouse disease. This microbe appears in the grouse as cocci and diplococci, many spherical, some also oval, few rod-shaped; but numerous cylindrical forms exist in certain artificial cultures (broth) and in guinea-pigs and mice, inoculated with them.

A special form of cocci is represented by *sarcina*. Under this name are understood those species of micrococci which, owing to a rapid and repeated subdivision of the cocci in vertical lines, form groups of four cocci and multiples thereof. When a coccus divides into a dumb-bell or diplococcus, and each of these again divides in a direction vertical to the previous one, a group of 4 cocci is formed—*Micrococcus tetragonus* (fig. 4). In these groups each two cocci are crescentic with one more or less straightened side, or they are even square cut; by further division of each coccus, the group increases from 4 to 8, 16, 32, and more; but in these the cocci are always more or less subgrouped in fours—*Sarcina lutea* (fig. 3). Now, some species of cocci show under certain conditions of growth this tetragonal arrangement or grouping in fours in a conspicuous manner, others show it only imperfectly; but even those that show it conspicuously under certain conditions show it less or in a not at all pronounced degree under other conditions of growth.

When owing to repeated division the cocci remain aggregated in larger or smaller groups, which themselves gradually extend as reproduction proceeds, and are connected by streaks of cocci in a more or less irregular fashion, such cocci are called staphylococci (*staphylis*, a bunch of grapes), to distinguish them from a species of cocci which, after division, remain joined in a linear series. By this latter method of division chaplets or chains of cocci are formed which, according to the number of subdivisions, are shorter or longer; such a chain-forming coccus is called streptococcus (*streptos*, bent, twisted), because generally these chains, particularly when long, are more or less wavy and twisted. In these chains the cocci are often arranged as dumb-bells, this indicating the actual phase of division or one immediately after; in others, the cocci are of equal distance, indicating the phase before division of the individual cocci has commenced. Always, however, one meets with individual cocci in chains which are considerably larger than the rest; these are found either in the chain or, more commonly, at one end; in the latter case they are sometimes club- or pear-shaped. Whether these larger cells represent a particularly active element or one that has undergone involution, is not easily to be made out. From what will be stated below of similar forms of bacilli, the writer is inclined to think that they are not involution forms, but indicate an altogether different phase, viz. atavism or a reversion to an antecedent form in the history of the evolution of the cocci.

2. *The Bacilli.*—All bacilli are rod-shaped or cylindrical cells, which differ one from another in the length and thickness of the cells. In the same species, as mentioned above, there occur the greatest differences as regards the length of the rods. While in a good many species, to be hereafter more minutely described, even the shortest or youngest elements are distinctly cylindrical, there are numerous species in which the youngest elements do not differ from spherical or crescentic cocci; these are then chiefly arranged as diplococci and represent a rapid mode of division of young elements; but there are present already in early stages elements which are distinctly cylindrical, and, as growth proceeds, these cylindrical elements increase in number and in length. We could name here a long series of species of pathogenic bacilli, which, when taken from the blood of an animal, or growing on gelatine or agar mixture, show in the earlier stages the majority of the elements as oval rods; some, like dumb-bells, constricted in the middle; but in broth cultures there are also noticeable numerous cylindrical elements in the early stages. After a few days' growth on solid media (gelatine, agar) numerous cylindrical elements are met with. Thus, the microbes known as connected with, and causing rabbits' and pigeons' septicæmia of Davaine and Koch, the organism of swine fever and of Wildseuche, of infectious fowl enteritis, of guinea-pigs' septicæmia, of fowl cholera, of the Middlesbrough (human) pneumonia, of grouse disease, the bacillus of Friedländer and several species allied to this, the bacillus pyocyaneus, the bacillus of veal and pork pie, and others when taken from the blood or tissues, or from early cultures on solid media (gelatine or agar mixture)—all these are like diplococci or slightly oval organisms; when examined, after a few days' growth on these media, they are in numerous individuals cylindrical, some four or five times longer than they are thick.

All these species taken from early cultures on gelatine or agar mixture, or from the blood and tissues, would in former years have been regarded as belonging to Cohn's group of bacteria proper. But also in species, about whose bacillary nature there never was any question, some individuals occur in all cultivations which do not differ from cocci and diplococci, being spherical or slightly oval cells, singly, or more commonly as dumb-bells; such is the case with the tubercle bacillus, with the bacillus of diphtheria, and with a variety of species of non-pathogenic bacilli. But here the question whether or not they are bacilli is at once answered by the occurrence in the same preparations of numerous, or even the majority of, cylindrical elements.

Now, the opinion has been repeatedly expressed by various observers (Naegeli, Lankester, Zopf, and others) that there exists no well-marked boundary between the different forms separated by Cohn as micrococci, as bacilli, and as spirilla, on account of the transitional forms between each of the two groups. As we have shown above, numerous species of bacilli exist, in each of which cocci, cylindrical forms and intermediate forms, do occur; but does this justify us in saying that between the *species* of micrococci and those of bacilli, intermediate species occur, and that there is no definite boundary between them? Clearly not. In those species that are micrococci, the elements, under every condition of growth that has been tried, always appear as cocci, either singly or as diplococci, as staphylococci or as streptococci, as the case may be, and never as cylindrical rods: these are clearly and decidedly species of micrococci. In some of the species of bacilli, on the other hand, the youngest forms may not be larger than a spherical or cubical mass of protoplasm, may therefore not differ morphologically from a coccus, but have the power to elongate into rod- or cylindrical-shaped cells; in other species, again, even the youngest elements are as a rule, cylindrical, although also here amongst these well-pronounced bacillary forms under certain conditions some elements appear almost spherical or cubical, e.g. bacillus anthracis, bacillus of tubercle, bacillus of diphtheria, as will be shown later on; and the same holds good also for some of the species which are spirilla, for, as we shall presently show, the youngest forms also of these appear as mere spherical or oval masses of protoplasm, capable of elongating into more or less curved rods and cylinders, and these by continued growth elongate into wavy or spirally twisted chains or threads. But because in a certain state they are like cocci, we shall not put them down as micrococci, and because between the cocci forms and the spirillar forms intermediate shapes occur, we shall not consider them as indicating a change of species, as if micrococci were to change into spirilla; but since in their adult phase they grow into spirilla, we shall call such species spirilla.

An organism has been minutely described by Zopf as *Cladothrix dichotoma*: in this organism there is no doubt that cocci, straight rods, isolated and in chains, and shorter or longer spirilla do occur, but it is not at all permissible to consider this as evidence that between the three groups of bacteria, viz. micrococci, bacilli, and spirilla, there is no definite boundary line. The cocci-form of the *Cladothrix dichotoma* when sown on the different media will again give rise to *Cladothrix dichotoma*, and will never become or grow as micrococci; and if the bacillary forms of this microbe are watched in their growth, it will be seen that some of them again give rise to spirilla. This same phenomenon can be easily ascertained in some of the typical spirillar species, e.g. the spirillum of Finkler, of Koch, the spirillum of noma. In all cultures, after a few days' growth, forms show themselves which do not differ from cylindrical bacilli, in which a curve of the rods is very slightly or not at all indicated; they appear as single rods, as dumb-bell rods, or as slightly wavy chains or threads, yet on further growth they are capable of becoming curved and assuming the spirillar form.

We conclude then that if a certain species under all conditions of growth is and remains spherical or nearly so, we have to deal with a species of micrococcus; if, on the other hand, a certain microbe grows into cylindrical elements more or less straight, it is a species of bacillus; and lastly, if it grows into curved rods and more or less spirillar forms, it is a species of spirillum.

Many species of bacillus form chains by linear arrangement, that is, the offsprings of one element after division remain attached one to another end to end; these chains may be composed of few or many rods, according to the number of subdivisions that have taken place; and in this way short or long threads may be formed. These are spoken of as leptothrix. Some species of bacillus have this power of growing out into threads in a very high degree; these species are very numerous, and their type is represented by the bacillus subtilis of hay infusion, and by the bacillus anthracis. The threads are either more or less straight or wavy and often like coils, the individual threads being more or less twisted one round another. When viewed in the fresh state they appear smooth and uniform, but after staining, they, like the shorter and shortest chains, are seen to be really only linear series of rods or cylinders. In such chains the individual cells are more or less of uniform length and thickness; but there are not wanting such chains and threads, in which successive or distinct elements differ considerably in length and also occasionally in thickness. Fig. 14 shows threads composed of rods of equal length and thickness; fig. 19 shows threads of the same species, in which the elements show a difference both in the length and thickness. Particularly the difference in the length of the rods is instructive, since 9 it shows that this is merely a phase of development; the most recent divisions or the youngest forms being shorter, cubical, or even like cocci, the older forms more cylindrical. This is also very well pronounced in tubercle bacilli, as will be illustrated below. Occasionally in a chain the rod-shaped elements follow one another as dumb-bells, evidently indicating a phase of simultaneous division of the cylindrical elements of a chain.

When bacilli are stained with aniline dyes and then sufficiently washed, they all show certain well-marked appearances: (1) the sheath, (2) the protoplasmic contents. The sheath appears as a thin faintly stained investment. When bacilli are arranged in dumb-bells or double-rods, or in shorter or longer chains and filaments, there is always a thin septum passing between two serial rods; the whole chain or thread appears invested by a common continuous sheath from which pass transverse septa which separate the individuals crossways; it is also noticed that the protoplasm of the individual rods is as a rule in much closer contact with the sheath than with the transverse septa. The protoplasm is either uniformly stained, or, as is not uncommon, it shows at the ends of each rod much deeper staining than in the middle, that is to say, there is denser protoplasm at the ends of the rods than in the middle. In the short individuals this often gives a very characteristic appearance, inasmuch as each rod appears made up of three parts of equal size: two terminal stained granules and a middle clear unstained part. As just stated, this is not peculiar to any one species, but can be noticed in all species; it is particularly conspicuous in those in which the young elements are short, e.g. fowl cholera, fowl enteritis, septicæmia of rabbit, swine fever, &c., &c. (fig. 7). But also amongst the longer, i.e. cylindrical elements, the middle part of the rod very often appears unstained and clear, while the protoplasm at the end is denser and stained; the middle clear part is at the same time more or less well marked off with rounded outline, spherical or oval in shape, and represents a vacuole; occasionally the stained protoplasm is central while the unstained parts, the vacuoles, are terminal. Such vacuoles are very common in all species of bacilli; they (vacuoles) are, however, more frequently met with under conditions which imply want of sufficient nutritive material, as for instance when bacilli grow on solid media (gelatine, agar mixture, potato), and when, owing to the continued growth into the depth of the medium, the first formed or superficial layer becomes gradually removed from the nutritive material; in this superficial layer the vacuoles in the rods are very conspicuous; in preparations made of thread-forming bacilli under the above conditions of growth these appearances, i.e. the presence of vacuoles regularly disposed in the individual rods, are very striking (fig. 17).

But, as before stated, the presence of vacuoles in the rods is also found under other than the above conditions, in some species more numerously than in others, and more often where rapid growth takes place than where this is not the case. This vacuolation is not indicative of any degenerative change—any more than in the mycelial threads of fungi where it is well known and typical—but seems, in some cases at any rate, to be due to the medium in which the bacilli grow containing comparatively less nutritive material: not only in bacilli, but also in the individuals composing a spirillum are these vacuoles to be observed. In cylindrical bacilli these vacuoles may be, and sometimes have been, mistaken for spores.

The ends of bacilli are generally rounded, occasionally straight, and less frequently more or less pointed or conical at one or both ends. In bacillus anthracis the ends are generally more or less straight; in the bacillus of diphtheria grown on gelatine many bacilli show one end pointed, the other rounded or straight and thick.

In many species one or both ends of the rods, or the free end of the rods forming the terminals in a chain, are swollen and thick, spherical, round, pear-shaped, or club-shaped; occasionally there are some elements, in the middle of a shorter or longer chain, swollen, spherical, or oval. Such forms are considered as involution forms, but there are good grounds for doubting this, and the reasons will be stated later on in connection with the evolution of bacteria. When in a chain of rods, i.e. in a thread, the individual rods become so changed, an organism results which is totally unlike the typical thin smooth thread, but appears more like a varicose thread in which the individuals are torula-like, spherical, or spindle-shaped cells, connected by thin bridges, the cells being three or more times as thick as the typical rods (fig. 70). In connection with this and the former appearance, another appearance deserves notice, viz. the segregation of the protoplasm in a chain or in individual rods as separate spherical or oval granules, whereby the rods and chains become transformed into varicose rods or fibres; in these the granules take and retain the dye easily, whereas the bridges between them are less stained; in the tubercle bacilli, leprosy bacilli, diphtheria bacilli, and others this appearance is sometimes very regular and characteristic (fig. 78).

3. *The Spirilla.*—The individuals of spirilla are rod-shaped or cylindrical, but more or less curved, representing the arc of a smaller or larger circle; they are also called comma-bacilli,[1] their ends are rounded, or not unfrequently slightly pointed. As regards the amount of curvature there exist the greatest varieties, not only amongst the different species, but also within the same species. Thus, for instance, in the cholera spirilla, in Finkler's spirilla, and in spirilla which were found in the intestinal mucus of apes affected with diarrhœa, one sees some elements of the shape of small semicircles, while many others only just show an indication of a curvature. But the same species grown on different media shows remarkable differences as regards the curvature of the ends. When growing for several days the comma-bacilli form longer or shorter chains, which are wavy or more or less spiral; this depends obviously on the curvature of the individuals from which such a chain is derived. When growing in fluids, some species of comma-bacilli form well-pronounced uniform spirals; also in solids, some chains are more distinctly spiral than others, some being only slightly wavy, while others are uniformly spirally twisted—sometimes the turns of the spirals are very close, sometimes more open. The spirals are in some cases uniform, e.g. in relapsing fever, and it is difficult to show that they are made up of curved rod-like elements, while in others (cholera) many of the spirals are distinctly jointed. There exist very considerable differences in the thickness

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[1] The name comma-bacilli was first applied by Koch to the cholera spirilla, owing to their likeness in shape to a German comma, which is simply a slightly curved rod; the word cholera bacilli for these microbes is reprehensible, because they are spirilla and not bacilli.

of the spirals in the different species, and in the thicker species the jointed character of the spirals is more easily demonstrated than in the thinner species. The individual comma-bacilli in stained and well-washed specimens show the same distinction into sheath and protoplasm as was mentioned of the bacilli, and also the presence of a vacuole in the middle of the individual comma-bacilli and the terminal easily stained collections of protoplasm. Though in some species of bacilli, e.g. bacillus of glanders, bacillus of diphtheria, there exist rods which are more or less curved, they do not form spirals, and their curved character is not permanent; but in the true spirilla, however slight the curvature of some elements—and in some species and under some media the curvature of some of the elements is very slight indeed—they nevertheless are capable of forming spirals. Thus the writer has seen even anthrax bacilli growing on alkaline gelatine assuming a very markedly curved shape, while Finkler's spirilla, or those found in noma and in Asiatic cholera, appear in some media only to show the very slightest curve; but from subcultures of the above anthrax bacilli in broth or gelatine the typical straight anthrax bacilli result, while of the above spirilla subcultures made in broth, in gelatine, &c., the typical spirilla will be the result. This shows that the first, though they may occasionally become curved rods, are not spirilla but bacilli, and the latter, though the individuals may occasionally appear almost straight, are not bacilli but spirilla.

MOTILITY

One of the most interesting phenomena shown by bacilli is the power of active locomotion possessed by some species. When examined under the microscope in a fluid medium all bacteria show the kind of oscillation known as Brownian molecular movement; but in some species there is an active locomotion, by which the individual bacteria are enabled to move actively and to change their place; this movement shows itself either by the bacteria darting with great rapidity across the field of the microscope in one or another direction, or spinning round with greater or lesser velocity, or briskly moving like a screw in one direction and then back again. Observing a single straight bacillus in its movement, either a darting or spinning movement in one direction is noticed; when two such bacilli are connected endwise, but bent one to another under an angle, then often, with a forward or backward movement of the one, a spinning movement of the other is noticed, the former not really actively moving but being simply propelled by the spinning movement of the latter bent under an angle. When comma-bacilli or spirilla move, the motion is always more or less spiral.

When longer chains or leptothrix of bacilli move, the movement is always more or less serpentine. The locomotion of bacilli is either rapid or slow; the latter may be a character of the species, that is to say, the individuals as a rule show only a relatively slow movement, e.g. typhoid bacilli generally move comparatively slowly, and the longer bacilli move in a serpentine manner. The mobile individuals do not continue to move indefinitely, since often an individual which has been spinning round or darting about gradually comes to rest and remains so for some time; besides this, all motile bacilli during the phase of division are at rest, and when they form groups, i.e. when they are in an active state of division, they do not move. But of such groups here and there an individual may be seen to separate itself from the margin and to move briskly away; on breaking up a group, crowds of motile bacilli sally forth. The writer has watched single bacilli of the human Middlesbrough pneumonia spinning round with great velocity without much changing their place. One and the same bacillus was noticed to spin round for five minutes without any diminution in its velocity; then this gradually lessened, and ultimately, after further five minutes, the organism came to rest. When a drop of broth was added, the spinning-round commenced again with great vigour. Some mobile bacilli show motility under a certain condition and not under others; others again show it under all conditions. Thus, for instance, many individuals of the bacillus of the Middlesbrough pneumonia show active locomotion in specimens made of gelatine and agar cultures; made of broth cultures the motility of many individuals is observable only while the broth cultures are of recent date—24–48 hours old; later on only very few motile individuals are met with. The loss of motility may be and sometimes is due to chemical by-products in the cultivation (*see* bacillus of grouse disease and of pneumonia). Some species of motile bacilli when growing on a solid medium are capable by their locomotion of distributing themselves from a given point rapidly over and through the medium, e.g. certain species of bacilli known as proteus of Hauser, certain species of the potato bacilli, &c.; this phenomenon is spoken of as 'swarming—thus, when a colony of such bacilli appears on gelatine, agar mixture, or potato, irregular streaks and lines and patches of the growth are soon seen extending in different directions, this being due to the swarming of the bacilli from the first colony and the establishment of new colonies by the former. There exist great differences in this respect between different species of motile bacteria, for while some species do not swarm at all and their colonies on solid media remain localised and more or less well defined, though they gradually enlarge (e.g. bacillus subtilis, bacillus fluorescens, some species of proteus, and many spirilla), other species possess this swarming propensity, and therefore the first colonies do not remain well defined, but gradually extend in lines and irregular streaks in different directions. But it is not correct to conclude that a bacillus is motile if its colonies do not remain defined, that is, if they extend in the shape of threads or irregular streaks on or through the medium, for there exist several well-studied species which do this (e.g. bacillus anthracis, bacillus filamentosus), though their bacilli are not motile, as will be more minutely described when speaking of the cultural characters of bacilli.

When certain bacilli show only slight motility it may be extremely difficult to distinguish this from Brownian molecular movement, but no locomotion can be ascribed to bacilli unless one or the other individual can be distinctly seen to show a darting or spinning movement. As mentioned above, the easiest and best way to see locomotion is to examine the fresh bacilli in a fluid, as sterile broth or sterile salt solution in the 'suspended drop.'

The motility of bacilli and spirilla is due to their possessing at one, and occasionally at both ends, or also over the general surface, fine flagella or cilia, the movement of which causes the motility of the microbe. Where two or more microbes are connected into a chain or thread, only the terminals have the flagella. Although the flagellum has been seen and photographed only in the larger bacilli and spirilla, there can be no doubt that all motile organisms do possess the flagellum, for without it motility would not be possible. Micrococci are not possessed of motility, but recently Ali-Cohen has isolated from drinking-water a species of micrococcus (*Micrococcus agilis*) which forms an exception, since this species is motile ('Centralbl. für Bact.' VI. 2).

Important methods of demonstrating (staining) the cilia have been published by Löffler ('Centralbl. f. Bacteriologie und Parasitenk.' VI. Bd. 8, 9). Löffler points out and gives photographs of bacilli. vibrios, and spirilla which are possessed not of one, but a bundle of fine cilia at one end or over the whole body.

In most bacilli and spirilla which are possessed of motility this is intimately connected with a supply of oxygen. Though some species seem to obtain this readily even when in deep fluids (e.g. bacillus of hay, certain species of proteus), many others cease to move when the supply of oxygen becomes insufficient. Engelmann has made some very interesting experiments with certain motile bacilli, showing the direct influence of oxygen on their motility. When motile bacilli, owing to insufficient oxygen or after the consumption of the oxygen previously present, come to rest, by adding to them new oxygen in a drop of fresh fluid containing air, the motility is resumed. On removing the oxygen and adding carbon dioxide or hydrogen gas, ammonia, chloroform, or ether, the movement ceases, but on removing these gases and replacing them again by oxygen (or air) the movement is again resumed.

Motile bacilli and spirilla when growing in a fluid medium have a great tendency to seek the surface of the fluid, i.e. move towards the part where they can obtain oxygen, and here form more or less coherent pellicles, in which they are in a resting state, and in which a rapid multiplication goes on; but it is quite incorrect to assume that an organism which in a fluid medium forms a pellicle is a motile organism, since some species which form a pellicle are not motile, and some species of motile organisms do not form a pellicle.

CHAPTER II

CONDITIONS AND MODE OF MULTIPLICATION OF BACTERIA

Bacteria when planted on a medium containing the necessary ingredients, and when the other conditions, as temperature, moisture, reaction, &c., are favourable, multiply with great rapidity. Substances containing nitrogenous compounds, potassium and sodium salts, phosphates and sulphates, are to be considered as necessary ingredients. In regard to these substances both qualitatively and quantitatively there exist, however, very great differences indeed. While some bacteria are capable of growing and multiplying on simple nitrogenous compounds (e.g. tartrate ammonium, ammonia, urea, uric acid), many others do not show any growth under such conditions. Many common or saprophytic bacteria living in the soil, in putrid or ammoniacal urine, thrive well when only simple nitrogenous material is available; e.g. such as is present in normal urine; while those bacteria like the disease-producing microbes, as also those generally present in dead organic matter of the living or non-living nature, thrive well only in the presence of albumen or albuminoid nitrogenous material. Various species of bacteria (micrococci and bacilli) occurring in ammoniacal urine, in soil, and other substances show active growth when planted in a fluid that contains nothing more complex than tartrate of ammonium (Pasteur's and Cohn's fluid); a great many species, amongst them all the pathogenic bacteria, do not show appreciable growth under these conditions. As regards the amount of the albuminous material, some species like those present in ordinary drinking-water, which contains only traces of albuminoid matter, are herein capable of multiplying, whereas others accustomed to live on more copious nitrogenous soil when transferred to such water gradually diminish in numbers, and ultimately, unless in the form of spores, altogether die. The greater the amount of albuminous material present the greater will be found, *cæteris paribus*, the capability of multiplication. As regards the lowest limit of proteid required for active and good growth there exist great differences, as great as those previously named ; for while the presence of albuminous material is to all bacteria a stimulation for multiplication, it is not, as stated above, absolutely essential to some. As a matter of fact there exist infinite gradations between species that require for good growth a comparatively large amount of highly differentiated albuminoid material—e.g. some pathogenic bacteria like tubercle bacilli—and those that can do well with very little of it. and even without it, but with only a little urea, or tartrate of ammonium—e.g. those in ammoniacal urine, those in soil, some of those in ordinary drinking water. More than that, there are at present some known species which can grow well on materials not containing any nitrogenous material at all ; thus the bacillus amylobacter or clostridium butyricum can grow well on no higher organic material than starch (Prazmowski). Some organisms in the soil multiply most probably at the expense of the nitrogen absorbed from the air (*see* below), and Macfadyean shows that some species of bacilli, though accustomed to live on albuminous soil, can nevertheless do well on pure starch paste. Some bacteria in drinking water—e.g. *Micrococcus aquatilis* (Niessen)—are said to be able to exist even in pure distilled water. Now in these cases it must be assumed that the nitrogen necessary for the building up of the protoplasm of their own bodies is obtained by the bacteria by absorption of free nitrogen from the air. The protoplasm constituting the principal part of the body of the bacteria is, like all other protoplasm, essentially albumen, and therefore, in order to grow and multiply, the bacteria have naturally to build up protoplasm ; and since this can only take place at the expense of nitrogen absorbed from the air (as in the cases just mentioned), or at the expense of simple nitrogenous compounds like salts of ammonia, urea, &c. (as in the cases of bacteria mentioned previously in putrid urine, water, and soil), it follows that some bacteria, at any rate, are capable of forming albumen by a process of synthesis, and in this respect, therefore, they compare with plants and not with animals. In the former this is the natural proceeding, while in the latter the protoplasm of the tissues is formed at the expense of the proteids taken in the first place with the food.

PROTEID MEDIUM

Most bacteria grow well in media containing 0·5 per cent. of proteid, less than is present in potato (1·5 per cent.) ; but there are some which show scanty or no growth on potato or in other media when only 0·5 per cent. proteid is offered. There does not seem any known reason why this should be so, but it is nevertheless a fact. Thus, one of the most highly differentiated microbes, like the glanders bacillus, grows well on potato, while, for instance, the diphtheria bacillus and the bacillus of fowl enteritis do not show any appreciable growth under the same conditions. This, however, does not apply to pathogenic microbes only, for some non-pathogenic microbes cannot grow on so small an amount of proteid as is present in the potato (1·5 per cent.).

SALTS

From the *presence of potassium salts and phosphates* in the bodies of bacteria the presence of these substances in the nutritive medium must be concluded as absolutely essential.

MOISTURE

An important influence on the growth and multiplication of bacteria is exerted by *moisture*, since their own bodies and the protoplasm constituting them contain water. Without a small amount of water no growth takes place. In fluid media the growth of all bacteria is, *cœteris paribus*, more rapid than on solids, and on these the growth varies, *cœteris paribus*, proportionately with the amount of moisture. It is easily shown that two solid media of the same kind, but differing from each other in the amount of water present, inoculated with the same species of bacteria will, after the same periods, and kept under otherwise the same conditions, show a remarkable difference of growth; the one that contains most water shows copious growth, while the other shows only comparatively little. For instance, on preparing two quantities of nutritive gelatine (meat juice peptone gelatine or broth peptone gelatine), one containing 97 per cent. water, the other 89 per cent., and inoculating these with various species all in double series, e.g. anthrax bacillus, staphylococcus, streptococcus pyogenes, bacillus subtilis, cholera spirillum, bacillus pneumoniæ, bacillus of fowl enteritis, bacillus of typhoid fever, or common saprophytic species, a notable difference will be noticed after two or three days' growth at 20° C.; those tubes containing gelatine with 89 per cent. water will show considerably less growth than those with 97 per cent. But it must be here mentioned that some bacteria are more sensitive to small amounts of moisture than others; for while some species show comparatively good growth when a small amount of free moisture is present, others show no growth unless the amount is considerable. Thus, for instance, many species like bacillus subtilis, and bacillus anthracis, various species of spirilla, grow well under the first conditions, while others, e.g. the tubercle bacillus, require for good growth a visible amount of moisture.

TEMPERATURE

Temperature plays an important *rôle*. Most bacteria show good growth between 18° C. and 38° C., and most between 30° C. and 37° C. Some show growth, but to a less extent, below 18° C., as low as 15° or even 14° C.; or to a higher extent above 38° C., as high as 42° and 43° C. Some few species are known that show good growth at a higher temperature, some even as high as 60–70° C., e.g. the bacillus thermophylus of Miquel, the micrococcus found in hot springs by Hoppe-Seyler. The most remarkable point about the bacillus thermophylus is that it ordinarily exists in the soil, and that nevertheless it shows very excellent growth and spore formation at temperatures even above 60° C.

Some species do not grow well at temperatures below 22° or 23° C., some not even below 30° C., or even 35° C.; to the first belong the diplococcus pneumoniæ of Fraenkel and Weichselbaum, a streptococcus occurring in the fluid of the mouth under normal conditions, a bacillus similar to but not identical with the bacillus of diphtheria, viz. the pseudo-diphtheria bacillus of Löffler; to the latter the tubercle bacillus, the leprosy bacillus, and to a lesser extent the glanders bacillus. Some species do not grow at temperatures above 22° or 23° C.; for instance, a micrococcus (streptococcus) which the writer isolated from certain infectious ulcerations of the teats of milch cows, a bacillus which he found in veal pie that had caused acute chemical poisoning (gastro-enteritis), and a bacillus which he found in dust taken from the plugging of the floor of dwelling-houses; these grow well at 20–22° C. in broth, gelatine, and agar mixture, but when exposed in these media to

25–30° C. no growth takes place. The bacillus prodigiosus, while growing well at temperatures below 25° C., does not grow at higher temperatures.

In ordinary drinking water, and in the air of dwelling-houses, there are many species of bacteria which grow well at 18–20° C., and at all degrees up to 38–40° C., but there are some that do not grow at temperatures below 25° C.; therefore testing for the presence and number of bacteria in water and in the air of dwelling houses by the simple gelatine plate method, in which the nutritive gelatine is kept at a temperature between 18°–22 C. (20° C. on the average), does not reveal all species present, since there are some which do not grow and multiply at these temperatures.

Air

Pasteur was the first who showed a radical difference to exist between different bacterial species in their requirement of free access of air during their growth and multiplication. He distinguished those that can grow without free access of air as anaërobic, the others as aërobic. At present when the mode of growth of the different bacterial species can be more accurately studied (owing to greater perfection in the methods of cultivation), the bacteria are capable of being grouped as follows: (1) obligatory anaërobic; these are such species as do not grow except when free access of oxygen (air) is excluded; such are the malignant œdema bacillus of Koch, the clostridium or bacillus amylobacter of Prazmowski, the tetanus bacillus, the bacillus of symptomatic anthrax; (2) facultative anaërobic, those species which can grow in absence of free air, though they grow better if air be present; these and the following form the majority of the species hitherto known; (3) facultative aërobic are similar, and the boundary line is indistinct; speaking generally, these grow better without free air, though they grow also, but not so well, when free air is admitted, i.e. on the surface of the nutritive medium; and (4) obligatory aërobic, those that do not thrive and multiply without copious supply of air; as, for instance, the hay bacillus, various potato bacilli. In the study of the obligatory anaërobic bacteria it is, of course, necessary to see that the seeding is carried out so that they are deposited at once in the depth of the solid medium, or that if seeded on the surface this latter is then covered up by a new layer of medium—oil or paraffin, or a layer of the same medium, e.g. a new layer of gelatine or agar;—or that culture tubes are used from which the air is removed by the pump, or replaced by some indifferent gas (H), and then sealed; or that tubes are used which are completely filled with the medium and after inoculation are sealed. But in all cases in which anaërobic bacteria have been grown, it is sufficient to see that the seeding takes place in the depth of the gelatine, away from the surface. The growth, then, takes place only in the deeper layers (*see* the figures of cultures of malignant œdema bacillus of Koch and tetanus bacillus).

Rapidity of Growth

The rapidity with which bacteria grow and multiply is subject to very great variations, and, *cæteris paribus*, constitutes definite and characteristic peculiarities; that is to say, some species under the same conditions of soil, temperature, &c., show a more rapid growth and multiplication than others, these bearing no relation to any known condition. Thus of the staphylococcus aureus and the streptococcus pyogenes, growing under exactly the same conditions, and on good nutritive media, the former shows incomparably greater rapidity in multiplication, and produces much more copious growth in a given time than the latter; or if the bacillus of swine erysipelas and the bacillus of swine fever be taken, the latter is found to grow much more rapidly than the former; and, again, bacillus subtilis and Finkler's spirillum grow very much faster than bacillus anthracis and cholera spirillum respectively.

Comparative experiments which the writer has made with a number of microbes as to the rapidity of multiplication, by way of observing them directly under the microscope in a drop of solidified nutrient gelatine at 22° C. ('suspended solid drop') show as the average of several observations—

(*a*) The streptococcus pyogenes. Complete division of the cocci took place in thirty minutes.

(*b*) The staphylococcus aureus liquescens in twenty minutes.

(*c*) The streptococcus of erysipelas in forty-five minutes.

(*d*) An orange-coloured non-liquefying micrococcus in forty minutes.

(*e*) The bacillus anthracis in thirty minutes.

(*f*) The bacillus subtilis of hay infusion in twenty minutes.

(*g*) A filamentous bacillus liquefying gelatine, not mobile and isolated from sewage, in eighteen minutes.

(*h*) A mobile bacillus (bacillus fluorescens liquescens), rapidly liquefying gelatine and common in ordinary London drinking water, in eighteen minutes.

(*i*) A bacillus, non-mobile, non-liquefying, rapidly forming spores, and slightly filamentous, isolated from London sewage, in forty minutes.

(*j*) The bacillus of the Middlesbrough pneumonia in eighteen minutes.

(*k*) The bacillus of fowl enteritis in twenty-four minutes.

(*l*) The bacillus of typhoid fever in thirty minutes.

(*m*) The bacillus diphtheriæ in forty-five minutes.

In all these instances a single organism lying isolated was focussed and watched, and after a distinct division had been noticed the time was marked, and the interval it took for one of these to again completely divide was taken as the time for a division. In these observations, which do not claim more than approximate accuracy, it was remarked that the division of the two members of the dumb-bell cocci or dumb-bell rods does not proceed at the same rate, the difference being as much as a quarter to a third of the whole time. The above numbers indicate the average of three successive divisions, and therefore they only represent approximately the mean periods that these several microbes require for dividing under the above conditions. Buchner ('Centralbl. für Bact. und Parasit.' II. No. 1) calculated the time required for the cholera vibrio for a division at 37° C., and found it to amount to twenty minutes on an average.

Observations were made on the common staphylococcus pyogenes aureus, the bacillus of swine fever, the bacillus of grouse disease, the bacillus of fowl enteritis, and the bacillus of diphtheria, as to the amount of multiplication these several microbes undergo when a definite number of them is introduced into faintly alkaline beef broth (eight to ten cubic centimetres) and kept in the incubator at about 37° C. All these different organisms grow with great rapidity, and after twenty-four hours the broth is uniformly turbid, provided the number introduced at starting be comparatively large. By making gelatine plate cultivations with a given small quantity of the broth previously diluted to a definite degree, and then counting the number of colonies that make their appearance on incubation, it is easy to calculate the number of microbes present per cubic centimetre in the broth. In some experiments made with the staphylococcus pyogenes aureus it was found that on introducing 248 microbes per cubic centimetre, they increased in the first twenty-four hours to 20,000,000 per cubic centimetre; in another experiment 640,000 per cubic centimetre were counted after the first twenty-four hours' growth, 248,000,000 per cubic centimetre after the second twenty-four hours, i.e. after forty-eight hours' incubation, and 1,184,000,000 per cubic centimetre after the third twenty-four hours i.e. after seventy-two hours' incubation. From a number of experiments it was calculated that for each microbe introduced, the multiplication during the first twenty-four hours is 80,000-fold, during the second twenty-four hours 400-fold, and during the third twenty-four hours 5-fold.

The rapidity of the growth and multiplication of the bacillus of fowl cholera in the living blood was ascertained in an experiment made on a rabbit. Of the microbes 20,000 were subcutaneously injected into a rabbit. The animal died in about twenty hours. The bacilli in the heart's blood were then counted by the ordinary method of gelatine plate cultivation, and it was found that their number per cubic centimetre of heart's blood amounted to 14,150,000. The weight of the rabbit was 1,250 grammes, and taking eighty-three grammes ($\frac{1}{15}$) as the amount of blood present in the animal's body, and assuming that the bacilli were more or less uniformly distributed through the blood, it follows that the total blood contained about 1,200,000,000 of the bacilli. This would mean that each one of the 20,000 bacilli injected had given origin to a host of 60,000 bacilli in twenty hours.

The manner in which the individuals of the same species divide varies considerably; thus in the streptococcus scarlatinæ and str. pyogenes the writer has observed that in gelatine some of the elements of a colony increase rapidly to five, six and more times the size of a typical coccus, grow, in fact, into a ball of great size, then a cleft appears by which the organism splits up into two demilunes, then each of these again divides under a right angle to the former line of division, so that the original ball is divided into four quarters, each of which separates gradually from its neighbour and becomes more or less spherical, and a further division into two and even into four cocci of the average size takes place. But the above mode of division does not take place everywhere in the preparation, for many of the typical cocci only slightly enlarge and then divide into two, thus forming a diplococcus; each of these divides again transversely, and thus a chain of four minute cocci is the result.

In broth cultures the writer has observed, as a rule, the latter mode of division, though also here occasionally an element is noticed in a chain which is much larger than the rest, and this larger element divides into two and four cocci successively. So also those large elements described above as occurring in the chains of streptococci show the successive fission into two and four cocci. And it is this which prompts him to say that these large elements found occasionally in the chains or in the diplococci are not involution forms, but are active elements which before successively dividing grow up to large size. In staphylococcus aureus liquescens, growing in gelatine, he has also observed some of these large elements, though on the whole they are not so numerous as in the streptococcus growing in the same kind of medium. The normal mode of division of a coccus is then (1) a slight enlargement and division into two by transverse fissure, or (2) a coccus enlarged to considerable size (four to six and more times) and then successively divided into two and four and further eight cocci of the normal size.

As regards bacilli, all observations hitherto recorded agree that a rod before dividing elongates sometimes more, sometimes less, and then a transverse indentation appears about midway, which ultimately becomes a fissure by which the originally single rod divides into two; according as the rod was short or long, the resulting offsprings are more coccus-like or more cylindrical. Now, in the observations which the writer has carried out as to the time of the division of the different microbes mentioned above, he has repeatedly noticed that a single cylindrical bacillus not infrequently divides almost simultaneously into three and even four short rods. The writer has observed cylindrical bacilli in preparations of bacillus anthracis, made directly from the blood of guinea-pigs, which were uniform, and there was no indication in the fresh specimen that they were other than single elements. These elements he has seen to give origin almost simultaneously to as many as four short slightly rod-shaped elements ; and these same elements were, on continued observation, seen to elongate and the terminals within several minutes seen to have increased almost to twice their length, then each of them again to have divided, one into three, the other into two distinct rods.

Observations were carried out on a filamentous bacillus isolated from sewage liquefying gelatine as a clear fluid ; it was non-motile, rapidly growing into threads, and in the filaments copious spore formation took place ; this bacillus resembled morphologically the bacillus anthracis, but it grows on the surface of gelatine more as a continuous membrane of threads arranged parallel and coming off at right angle from a central stalk ; it grows much more rapidly than the bacillus anthracis.

Now, directly observing under the microscope the growth and multiplication of this bacillus in solidified gelatine, threads of bacilli are seen shooting out with considerable rapidity from a short cylindrical bacillus measuring $0{\cdot}5\mu$, to 1μ, a thread more or less wavy is formed in the course of two hours and a half, which extends across the whole field of the microscope under a magnifying power of 500. On such a growing thread the simultaneous division after elongation of cylindrical elements into three and four rods is also distinctly and repeatedly noticed.

Also on the rods of the bacillus of diphtheria the same simultaneous fission of elementary cylindrical cells into two, three, and four elements was noticed. We conclude then that in the division of bacilli the elements increase in length and then by transverse fission divide into two, three, or four elements, and according to the length of the cell before division the elements resulting from the division differ in length.

SPORES

One of the most important and interesting phenomena in the life-history of bacteria is the power of some species to form *permanent seeds or spores*, by which the species can preserve itself and can withstand a variety of adverse circumstances. Various conditions in nature are often at play, in consequence of which weaker species are less liable to survive in the severe struggle for existence. There is first the adverse circumstance of competition, such as constantly obtains under the general conditions of growth in soil, in water, and in various organic materials exposed to contamination from air, water, and soil. Here numerous species find access and multiply, some more, others less easily, till all the available nutriment is exhausted. Some species, capable of forming spores, when this stage of the exhaustion of the nutriment has been reached, remain as spores and, till they are transferred by some means or other to new material, or till new nutriment is added, retain their power of again germinating and giving rise to a new crop of the same species, and this survival occurs even under severe adverse circumstances, e.g. the presence of various noxious chemicals, cold, heat, drying, &c. ; but those species that do not form spores retain life only under exceptionally favourable conditions ; as a rule, owing to the presence of acids or other chemicals, e.g. products of the growth of bacteria, and owing to drying, &c., they are easily deprived of life. This question of the formation of spores for the above reasons plays a most prominent *rôle* as regards infectious diseases. A few illustrations will easily show this. Take, for instance, the bacillus anthracis. This organism, although present in enormous numbers in the blood and blood-vessels of animals dead of the disease, does not at any time form spores when kept away from the air, i.e. from a supply of oxygen; consequently in such an animal when left unopened all the bacilli, after having gone on increasing in numbers after death for some time, gradually degenerate and disappear, so that sometimes after five to eight days, in the case of small animals like mice and guinea-pigs, living anthrax bacilli are no longer to be found in the tissues, they having been suppressed by putrefactive organisms. The spleen of such an animal after this distance of time produces no infection with anthrax after inoculating it in comparatively large doses into a fresh guinea-pig or mouse; whereas if a trace of a droplet of the splenic blood of an animal dead of anthrax is used for inoculation of a guinea-pig or mouse, say within three days after death, virulent anthrax follows. Or if the blood and tissues of an animal dead of virulent anthrax are by some means or other thoroughly dried, such blood loses all virulent power, since by thorough drying the bacilli anthracis are killed. But let either the blood or the nasal or other discharges of an animal dead from anthrax be exposed to air for a sufficient time to allow the bacilli to form spores, then neither putrefaction, nor drying, nor chemical agencies such as acids and alkalies, will affect the power of these spores to germinate again into bacilli and to produce virulent anthrax when finding access to a suitable animal body. This is actually the case when cattle and sheep are sojourning on and feeding in a field, where months or even years previously an animal having died from anthrax, the blood and discharges of such an animal found access to the surface of the soil, that is where the bacilli anthracis find opportunity to multiply and to form spores. It is these spores which afterwards are picked up by the animals grazing in such a field. The same thing occurs in woolsorters' and hidesorters' disease, which is virulent anthrax in the human beings engaged in the sorting of wool or the handling of hides derived from animals—sheep, goats, and cattle respectively—which had succumbed to fatal anthrax. In these cases it is always spores of the bacillus anthracis which are the cause of infection of the human beings handling these articles. Or take another illustration as regards putrefactive organisms. In preserving various articles of food, these articles are often subjected to the temperature of boiling water for variable periods from a few minutes to a quarter of an hour or thereabouts. Although all micrococci and bacilli not bearing spores are killed by such exposure, the spores of some species are not killed by such a temperature, and therefore if such spores happen to be present before the exposure, the spores will remain unaffected by the exposure to that temperature, and afterwards will be able to germinate into bacilli, which by their multiplication cause a very undesirable change in those articles. Cohn found in tinned peas some species of bacilli whose spores withstood the temperature of boiling water for thirty minutes, and although these must be considered exceptionally resistant spores, nevertheless there exist not a few species of bacilli whose spores can successfully resist the exposure to 100° C. for two, three, and even five minutes; an exposure to 95° C. some resist for nearly an hour; in fact, the writer knows of spores of several species which withstand easily such an exposure, amongst them the spores of bacillus subtilis and bacillus anthracis. But no micrococcus or non-spore-bearing bacillus can withstand exposure to 70° to 75° even for a few minutes; many of them are killed at 60° C. or even 58° C. in five minutes.

The presence or absence of spores is then, for the various reasons indicated above, of great practical importance.

Observing bacilli, which do form spores (e.g. bacillus subtilis, various species of 'potato bacillus,' bacillus mesentericus, bacillus anthracis, and the bacillus filamentosus above mentioned), it is noticed that the first sign of the appearances of spores is indicated by the presence of a bright, glistening globule in the protoplasm of the bacillus; at the same time the bacillus is distinctly broader and paler in its substance as compared with the other bacilli. This globule gradually enlarges in diameter, becoming at the same time slightly oval; this continues till the thickness of the globule often exceeds the breadth of the bacillus, this latter being now markedly pale and transparent. The writer has watched in bacillus anthracis and bacillus filamentosus the spores from their first appearance as bright globules till they had reached their full thickness and length; this took about three hours, and he has also noticed that after sowing on the surface of solidified agar the blood of the heart or spleen of a guinea-pig dead of anthrax and keeping it under observation at the temperature of 20° C. spores would be noticed in a few of the bacillary filaments after twelve hours; in the case of the bacillus subtilis, various potato bacilli, and bacillus filamentosus growing in broth, copious spore formation was noticed in a superficial pellicle after sixteen hours. Koch first observed that spore formation in bacillus anthracis occurred after six hours. But not all bright granules that make their appearance in bacilli are spores; thus in the typhoid bacillus growing on potato, and in other species of bacilli growing on potato, there appear bright granules, either terminally or centrally, which are not spores; they do not show the reaction of spores, either to dyes, or on drying, or heating. Nor are all the bright granules that make their appearance in bacilli capable of forming spores to be at once taken as spores, since under certain conditions such granules do occur, but never reach the size of full spores; this is observed occasionally in anthrax bacilli when growing under conditions unfavourable for the formation and development of spores. The appearance of real spores in all bacillary species is very characteristic; the spores are of a bright, glistening aspect, are oval in shape, and generally thicker than the typical bacilli. The substance of these latter is at the same time pale and transparent and broader than the bacilli not containing spores; the threads of the bacilli appear beaded by the spores, the beads being the glistening oval thick spores, while the rest of the thread is pale and appears thinner. In the single bacilli the spores are placed either centrally or terminally; in the latter case, if the bacillus is of some length, it looks not unlike a spermatozoon, the spore corresponding to the head, the bacillus to the tail. Sometimes in motile bacilli short chains are noticed, in which, in one terminal element, a spore has already made its appearance, while the other bacillus is still possessed of motility; and here, on account of the motility, the resemblance to a spermatozoon is still more striking. Under the most favourable conditions almost every element constituting a bacillary thread or chain forms a spore, in other threads only here and there a cell contains a spore; in the first case the thread is regularly and densely beaded, in the latter the beads are relatively few and far between. The last phase is reached when the bacillus itself swells up into a gelatinous capsule enveloping the spore and ultimately altogether disappears; then the spore is free and has reached its full size and development. Examining in stained specimens spore-bearing bacilli, the spores appear unstained, whereas the rest of the bacillary substance takes readily the dye; under these conditions the spore looks like an oval clear space, not unlike the vacuoles above mentioned; but the spore has a sharp outline of its own, the vacuole has not. It is, however, not easy to distinguish in a given specimen, stained after the ordinary methods, the spores which are not stained from vacuoles, and in these cases other methods of staining must be resorted to.

In order, then, to decide whether or not spores are present in a bacillary species, the morphological investigation, fresh aspect, special methods of staining, drying, and heating have to be resorted to.

The spore formation is associated with supply of oxygen in all bacteria that generally live well under access of air; in some species this is more pronounced than in others, for in some species, e.g. bacillus anthracis and bacillus filamentosus, spores are only formed, *cæteris paribus*, if oxygen has free access, and no spores are formed if there is no free supply of oxygen, e.g. deep in the fluid; while in other species, though spore formation is greatly enhanced by the free access of oxygen, it nevertheless takes place to a certain limited extent deep in the fluids. Thus, in the case of bacillus subtilis and various other bacilli a pellicle soon makes its appearance on the surface of the fluid (broth, &c.). This pellicle is made up of filaments and bacilli matted together, and in them copious spore formation is going on, but also in the depth there are a few spore-containing bacilli to be noticed. When such a pellicle is broken up by shaking, it in most instances falls to the bottom of the fluid, and then after another day's growth a new pellicle appears, and in this also copious spore formation is noticed; and this can be repeated for several days till the nutriment is exhausted. The same can be seen in hay infusion, in the case of bacillus subtilis. In neutral or faintly alkaline hay infusion kept at 37° C. spores of bacillus subtilis are present in the pellicle as early as the second day, and continue to be formed at the end of eight to ten days. The view has been expressed by some observers, amongst them Buchner, that the spore formation in bacilli occurs on exhaustion of the nutritive material, but it seems that the facts just mentioned as to the continuous and successive pellicle and spore formation occurring in broth are incompatible with that assertion; and, besides, the formation of spores in other bacilli can be shown to take place long before any exhaustion of the nutritive matter is noticeable, e.g. in anthrax bacilli, in the tetanus bacillus, and others. In the bacillus filamentosus, growing on agar or on potato, the spore formation is apparent even before the first day is over and long before the active growth and multiplication of bacilli all round is finished. In some species, however, that do not thrive under free access of air (e.g. œdema bacillus, tetanus bacillus) spore formation does not take place if free oxygen is present. A temperature of at least 16° C. is required for the formation of spores, though spore formation occurs in all temperatures between that and 45°; at least, spore formation has been seen to occur in bacillus anthracis even at 45° C. The mode of spore formation hitherto described is that of endo-spores, and it ought to be here stated that many species of bacilli exist in which no spore formation can be demonstrated—in this statement we rely on the morphological as well as the experimental test—e.g. typhoid fever bacillus. bacillus of glanders, of diphtheria, of fowl cholera, fowl enteritis, and many others. So far as actual demonstration is concerned, no other mode of spore formation can be accepted at present. A mode of formation of spores is described by Hueppe to occur in certain spirilla, according to whom the comma-shaped elements and the spirilla form special aggregations of protoplasm in the shape of terminal granules, to which the value of spores is ascribed, and which are called arthro-spores. But the evidence and proof for this is quite unsatisfactory, and, judging these appearances in the light of the characters of well-ascertained spores of other bacilli, they are contrary to the assumption of spores. These arthro-spores of Hueppe do not look like spores, do not behave in staining like spores, and do not behave in drying and heating experiments like spores. In the first place they do not differ in aspect from ordinary protoplasmic granules observable in some of these bacilli under all conditions; they stain in the ordinary dyes and after the ordinary methods like the ordinary protoplasmic contents of bacteria; and they are killed by drying and exposure to 60° C. for five minutes.

It can be easily shown that artificial cultures of these comma bacilli growing under conditions very favourable for the formation of real spores in other bacilli, e.g. a good supply of oxygen, temperature, soil, and moisture, contain after some weeks and months those granules or supposed arthro-spores in enormous numbers; in fact, there is almost nothing else left, and yet no sub-cultures can be established from such a culture, it being barren of all life. Structures have been described also in the typhoid bacilli as occurring in potato cultures, which can be, however, shown by special modes of staining to be different from real spores, and the experimental test of drying and heating conclusively proves that they are not comparable to spores.

On the other hand, the tubercle bacilli have been shown experimentally (by Koch and others) to possess spores, although it seems difficult to identify them under the microscope. True, there are present in microscopic specimens made of fresh material, e.g. tubercular sputum, bright granules within many of the bacilli which might be taken for spores, and in specimens stained after the customary method of staining for tubercle bacilli, numerous stained granules occur in the bacilli—the bacilli appearing beaded—but, as has been stated above, most of them are merely elementary masses of protoplasm segregated in the bacilli. They occur in some tubercle bacilli more numerously than in others, e.g. in the tubercle bacilli of the human subject they are common; in the tubercular material of the fowl and in artificial cultures they are sometimes seen with great regularity, but there is no means available of identifying these granules with spores. But by thorough drying of tubercular material it can be shown that the tubercle microbes remain uninjured, and that heating them up to 100° C. for a minute leaves the tubercle bacilli unharmed.

Spores have been described also of some micrococci, but here again certain differentiation of structure cannot be taken as proving the existence of spores. The writer has examined very numerous preparations of the most varied cultures of different species of micrococci, and the test of drying and heating to 70° C. proves them barren of anything comparable to the well-known spores present in some species of bacilli. He also examined experimentally various species of spirilla, and agrees with Koch that no spore formation can be demonstrated in them. We arrive then at the conclusion that real spore formation, or the formation of permanent seeds capable of retaining life under very adverse conditions, and under favourable conditions capable of germinating and of giving origin to a new brood of the same species, can be shown to exist only in certain limited species of bacilli, but not in micrococci or spirilla. These real spores are endo-spores, they are formed within the protoplasm of the bacillary elements under favourable conditions, and they have certain definite morphological and experimental characters of their own, at the same time representing as it were the last phase in the life-history of these bacilli. Bacilli or bacteria not capable of this power of producing spores, though they go on multiplying as long as the conditions of nutriment, temperature, chemical by-products, competition, &c., permit of it, ultimately degenerate, some sooner, some later. To propagate their species they must as living bacilli find access to new soil before the stage of degeneration is reached, whereas in the spore-bearing bacteria their spores can remain dormant, but possessing potential life for indefinite periods.

The statement has been occasionally made that spores are capable of dividing, and thus giving origin to two new spores. The writer has not been able to detect anything of this sort; he has never seen any appearances that would indicate such a division. True, in bacillus anthracis, in bacillus filamentosus, and in some species of 'potato bacillus,' spore formation may be going on so copiously that at some places every element constituting the threads contains a spore, some of the spores closely adjoining one another, sometimes so closely that it looked as if they were the two elements of a dumb-bell, and here a division of one spore into two could be thought of; but in these places the elements of the threads were extremely short and the spore occupied the main part of each element. It is also a fact that spherical globules occurring in some bacilli and being in aspect and staining power comparable to young phases of spores, are occasionally met with as dumb-bells within the same element; but as regards the oval, bright, unmistakable spores so prominent in the bacilli and their threads (bacillus anthracis, bacillus subtilis, bacillus filamentosus, bacillus mesentericus, &c.), it is very doubtful whether they are capable of dividing or of undergoing any other change than that of germination into bacilli when they are transferred to new soil.

Spores when placed under suitable conditions germinate again into bacilli. This is easily observed if, for instance, a trace of any culture-material containing spores is placed on a cover-glass, then covered with a tiny droplet of gelatine which is made to set rapidly, or in a droplet of broth ('suspended drop'), and is then observed under the microscope, particularly in the latter medium, which can be kept on the warm stage heated to 37° C.

Spores while fresh have a conspicuously sharp and dark outline, their general aspect is glistening, and it is supposed by Cohn that they are possessed of a double envelope, an inner one of a fatty and an outer one of a gelatinous nature: it is particularly the former which provides the spores with their great resistance to drying and to heat. The first indication that the spores are going to germinate is shown by their outline becoming less sharp at one point. This is generally at one of the poles, as in the case of the spores of bacillus anthracis, bacillus filamentosus, and bacillus subtilis; or it is at one point of the long side, e.g. in bacillus amylobacter, and also in the spores of some of the species collectively spoken of as 'potato bacillus;' the investment seems to become thinner at that point and a slight pale knob appears there. This knob gradually elongates in the form of a pale rod thinner than the spore itself; as it elongates, it protrudes more and more from the rest of the spore, its free end being rounded, while at the same time the rest of the spore outline becomes thinner and less dark; ultimately the whole spore has been consumed as it were in the formation of the rod, which now looks like a cylindrical bacillus of the same character and aspect as the bacilli from which originally the spore had been derived. The bacillus once formed divides and then continues to grow and multiply. The time required for the production of a bacillus from a spore varies with the different species. Koch observed the germination of the spore into a bacillus anthracis to be completed in about an hour; the writer has observed the time required for the complete formation of a bacillus from a spore of the bacillus filamentosus in broth, in the 'suspended drop,' at 37° C. to be certainly less than one hour; that of bacillus anthracis between one hour and a half and two hours; that of the bacillus subtilis of hay infusion to be more than one-half but less than one hour. Occasionally one meets in these observations with motile bacilli to which a spore which has not yet commenced to germinate is attached and is dragged about by the former: this evidently indicates that of two spores originally joined by interstitial material (*see* spores in threads), only one has already changed into a motile bacillus, the other has not yet so changed.

As must be obvious from the examination of micrococci, bacilli, and spirilla in fresh specimens, the differentiation of the various species belonging to each of these three great groups is based on a number of points which, in some cases, are easily detected, but in others only with great difficulty. As regards micrococci, where the difference in the size of the microbes belonging to different species is conspicuous, the diagnosis is not difficult; likewise in the case of bacilli where some species are motile, others not; or where some bacilli have in a prominent degree the capability of growing into threads or of forming spores, others not; or where some micrococci easily and readily form chains, others not—in all these the diagnosis is not difficult. But from what has been said in the foregoing pages it must be evident that there are a good many species of micrococci, bacilli, and spirilla, which, though totally distinct amongst themselves, as will be presently shown when describing their cultural characters, are, nevertheless, in all the above points alike. In such species we may find, for instance, great resemblance in size and aspect; and we may find in the case of micrococci that they are alike capable of forming chains, or in the case of bacilli that they are similar as to size, motility, power of forming threads and spores; and in the case of spirillum that they are alike as to size, aspect, and motility. Or, to take another character: some species of micrococci and bacilli are capable of forming pigments; now, not a few of these form apparently the same kind of pigment and also under the microscope look very much alike, yet it can be shown by other methods that they are different species. This differentiation is possible by observing the mode of growth of these microbes on artificial culture media, and their different characters on and in these furnish in most instances a ready and conspicuous means of diagnosis and differentiation. These characters are generally spoken of as *biological* characters, to distinguish them on the one hand from purely *morphological*, such as are exhibited by them under microscopic examination, and, on the other, from *physiological*, such as can be ascertained by taking into consideration their chemical activity and their influence on living or non-living (organic) matter. Before entering on the study of these biological characters we shall give a short account (1) of the methods used in studying the morphological, and (2) of the methods used in studying the biological characters of bacteria.

CHAPTER III

STUDY OF THE MORPHOLOGY OF BACTERIA

Examination in the Fresh State

The first and simplest, and at the same time a very interesting study is the study of bacteria in the perfectly fresh state under a sufficiently high magnifying power (300–500 diams.). Hereby the shape, size, motility, and general aspect are observed. The preparation is made by placing a drop of the material (artificial culture, tissue juice, or blood, as the case may be), or if solid by placing a trace in a drop of neutral (0·75 per cent.) saline solution or water previously sterilised by boiling, on a glass slide, and then covering it with a cover-glass. Shape, size, motility, and spores are easily observed by this method of study. An important method for observing the growth, multiplication, formation, and germination of bacteria and spores is the study in the 'suspended drop.' This means that a drop of the sterile nutritive material containing the bacteria is placed on a sterile cover-glass. This is fastened by sterile oil, wax, paraffin, or shellac on an object-glass over a shallow pit cut out of it, i.e. Koch's hollow glass slide, or over a low glass ring cemented to the object-glass. The simplest method is the one used in the observations mentioned above on the period required for division of the different bacteria. It is this: With a sterile platinum needle a very tiny trace of the bacterial culture is deposited in the middle of a clean and sterile[1] cover-glass; then to it is added a thin film of gelatine or agar deposited with a sterile glass rod from a test tube containing sterile nutrient gelatine or agar on the point of liquefaction. The film sets almost instantaneously. The cover-glass is inverted, and fixed on in the above manner to a low glass ring cemented on to a glass slide. Since the bacteria are near the under-surface of the cover-glass, the observation can be made with high powers. If the observation requires a temperature higher than that of the room, up to 37° C., the glass slide is kept on a warm stage.

Staining of Bacteria

In the next place the bacteria are studied in stained specimens: (*a*) in cover-glass specimens, and (*b*) in sections. The cover-glass specimens are prepared, after the Weigert-Koch method, by carefully spreading a thin film (the thinner the better) of the culture, tissue juice, blood, &c., pure or after dilution with sterile salt solution, over the middle of a clean cover-glass. Where the material is fluid or semi-fluid, this of course can be done without the addition of any fluid; but where this is not the case, a particle of the matter to be examined is distributed in a droplet of sterile salt solution and rubbed in a thin film over a cover-glass. Then this film is rapidly dried by holding the cover-glass over the flame of a spirit lamp or gas burner, but care is taken that no over-heating or charring takes place; the heating ought to be carried to such point that touching the palm of the hand with the cover-glass is just bearable. If the heating is not carried to a sufficient degree, the danger is that, besides the bacteria, also the ground substance (plasma of blood, the matrix of tissues in which bacteria are present, broth, gelatine, &c.) becomes stained; if the heating is carried too far, even if there is no charring, the danger is that nothing will stain distinctly. Passing the cover-glass rapidly three to ten times through the top of the gas flame is generally sufficient, or with great advantage the cover-glass after drying is steeped for a few seconds in acetic acid (1 : 2 or 3 of water), then washed in water and dried again. Then the cover-glass with the side containing the film is placed over the solution of the dye contained in a watch-glass, and left there for the time required to well stain the bacteria. This time is very variable in the case of the different dyes, and in that of the different bacteria, and must be learnt by practice and by experiments almost for each case separately, as it is impossible to state any hard-and-fast rule that would apply to all conditions. But there are certain rules of thumb which might be useful in a general way: The dyes that are very useful for almost all cases, with few exceptions, are: gentian violet, methyl or methylene blue, fuchsin, Spiller's purple, and rubin. Gentian violet, fuchsin, or methyl blue are with great advantage used mixed with aniline water; fuchsin, gentian violet, or methyl blue are very useful with carbol water, rubin, and Spiller's purple as 2 per cent. watery solutions. Aniline water dyes are made thus: Water is saturated by repeatedly shaking it in a bottle with aniline oil and letting it stand for several days; of this 100 c.c. are taken: to them are added 11 c.c. of a saturated alcoholic solution of fuchsin, or gentian violet, or methyl blue, or methyl violet: Mix well, and filter into a stoppered bottle (Weigert's dyes).

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[1] A sterile cover-glass is always understood to be a cover-glass which has been sterilised by passing it through the gas flame several times or holding it above it for several seconds.

Carbol fuchsin, carbol methyl blue, or carbol gentian violet are prepared like aniline water dyes, but instead of the saturated aniline water saturated carbol water (1 in 20) is used.

A 2 per cent. watery solution of a dye is made thus: 2 grammes of the solid dye are rubbed up in a mortar with 10 c.c. of absolute alcohol; then, while mixing over a flame, 100 c.c. of distilled water are gradually added till all is dissolved.

In many cases methyl blue is used with great advantage after Löffler's method, viz. methyl blue (saturated watery solution) with equal volume of potassic hydrate (1 in 10,000).

Gentian violet, methyl blue, methyl violet, fuchsin, Bismarck brown, or vesuvin, rubin, iodine green, dahlia, Spiller's purple, Victoria violet, and a host of other basic aniline dyes are used; some, like methyl blue, methyl violet, gentian violet, Humboldt's blue, and Humboldt's violet, and fuchsin, are useful sometimes as saturated watery, sometimes as saturated alcoholic, solutions.

The cover-glass specimens are left in contact with the dye for from a few minutes to several hours—sometimes exposure for as many as twenty-four hours is required. Keeping the cover-glass with the film downwards over the dye in a watch-glass covered up with a second watch-glass at a temperature from 35–40° C. increases in all cases the progress of staining; holding it carefully over a flame till the dye begins to steam requires only a minute or so; where in a given case twenty to thirty minutes are sufficient for achieving a result when the staining is carried on at the ordinary temperature, five minutes at 37° C. produces the required result; when one to two hours, at ordinary temperature, are required, twenty to thirty minutes' heating to 37° C. produces the result. Many if not most bacteria in cover-glass specimens stain sufficiently well, in Weigert's gentian violet, in Weigert's methyl blue, or in carbol fuchsin in fifteen to thirty minutes at ordinary temperature, in five to ten minutes at 37° C., in a minute or two at 65° C. Then the cover-glasses are removed from the dye, well washed in common water—warm water being better than cold—then distilled water, next dried to remove all water, and mounted, film downwards, in a drop of Canada balsam or dammar varnish. The cover-glass is ultimately sealed down on its edges with a narrow thin layer of Hollis' glue.

In some cases after washing with water, a good but rapid washing with alcohol to remove the excess of the dye, and to bring out finer differences of structure, is required. In some few cases this is not practicable, since the alcohol too easily removes the dye from the bacteria themselves, thus, in the case of spirilla the washing in alcohol must be carried out very carefully, i.e. very rapidly, one dip in alcohol being sufficient. In other cases this washing is not required, e.g. when staining with methylene blue, whereas when staining with Weigert's gentian violet the washing in alcohol is often necessary in order to remove the dye from all except the bacteria, this dye having the undesirable faculty of seizing upon everything present in addition to the bacteria. But whenever the process of heating the cover-glass specimen in the first instance has been carried out successfully, and the staining has not been overdone, simple good washing in water is sufficient to insure a satisfactory result. A successfully stained cover-glass specimen should show the bacteria alone conspicuously stained; also when nuclei of tissue cells are present these are well stained, but no tissue fibres, tissue granules, mucus, fibrin, or other ground substance should have the stain.

In order to stain cover-glass specimens with two dyes it is best to use one stain after the other, the two stains being a contrast in colouration: red and blue, blue and red, blue and brown, red and brown. Contrast stains are: violet (gentian violet or methyl violet) and vesuvin, methyl blue and eosin, methyl blue and fuchsin, methyl blue and vesuvin, fuchsin and vesuvin, rubin and methyl blue, or *vice versâ*. If it is desired to demonstrate in different and contrast colours different parts of bacteria, e.g. the capsules and the bacteria themselves, the bacteria and their spores, granules in bacteria and their protoplasm, or the bacteria and the tissue-elements (blood corpuscles, pus-corpuscles) present in the specimen, double-staining is resorted to. The cover-glass specimen after heating is stained in one dye, then washed in water, alcohol, very dilute nitric or other acid (HCl or acetic) as the case may be, or treated in decolourising reagents, e.g. carbonate of potash, iodine, ferrocyanide of potassium, &c. (*see* below), then stained with the contrast stain, washed, dried, and mounted. For a successful double staining the proper degree of staining and washing with each dye must be carefully attended to, and for this purpose preliminary experimenting is essential, for what yields success in one case does not in another. To illustrate this point by different examples: (1) Anthrax bacilli of blood. A thin film of blood of spleen or heart of an animal dead of anthrax is spread out on a cover-glass, dried, and well heated, then this cover-glass is placed in Weigert's methyl blue or carbol methyl blue; after thirty minutes at ordinary temperature the cover-glass is well washed in water, and then placed in an alcoholic solution of eosin; herein the specimen is left for a few seconds to half a minute, then washed in water, dried, and mounted in balsam; the bacilli anthracis and the nuclei of the white blood-corpuscles are in many places deeply blue, the red blood-corpuscles bright red; in some places the blue has been altogether driven out by the red from all bacilli and blood-corpuscles. The point to be attained is that the blue is driven out from the red corpuscles only; if too little staining in eosin, then also the red blood-corpuscles have a bluish colour: the point to be avoided is driving out the blue from all bacilli and blood-corpuscles. Reversed use of methyl blue and eosin often yields good results. A simple and excellent method of double staining is the following: Cover-glass specimens are prepared by well drying a thin film of the material: blood, spleen juice, lung juice, pus, &c.; they are then placed in a 2 per cent. watery solution of rubin, kept there for half an hour or more at ordinary temperature—if warmed to 40 or 50° C. ten minutes suffices—then washed in water and placed in methyl blue aniline water (*see* above) for one-half to two minutes. In this, however, different bacteria differ, for while some take up the blue rapidly, others do it less so; if the cover-glass specimens have been stained for hours in rubin, the time for the second or blue staining can be extended to a few minutes. Then wash well for a few minutes in distilled water, dry, and mount in balsam. The red blood-corpuscles are stained pink, the bacteria deep blue; leucocytes and other cells are pink in their substance, blue in their nuclei. By staining the cover-glass specimens first in rubin the bacteria present take up afterwards the blue much more readily than if stained directly in blue. By this method the writer has obtained excellent and beautiful specimens of a large number of bacteria in fresh tissues. (2) A cover-glass specimen of anthrax blood is stained in gentian violet aniline water or in ordinary watery solution of gentian violet or methyl violet for thirty minutes, washed in alcohol, then placed in a dilute solution of iodine in iodide of potassium for a few seconds till the colour of the specimen changes into purple, then washed in alcohol and placed in a solution of eosin or vesuvin for a few seconds to half a minute, next washed in water, dried, and mounted in balsam: the bacilli are blue, the blood-corpuscles are red or brown: this method is the method of Gram. (3) A cover-glass specimen of the capsulated bacillus of Friedländer is stained in methyl blue aniline water, washed in alcohol, next kept in alcoholic eosin solution for several seconds (ten to thirty), then washed in water, dried, and mounted in balsam: the bacilli themselves are blue, the capsules are pink. (4) A particle of tubercular sputum, or tubercular deposit of any organ, is spread out in a thin film on a cover-glass, dried, and heated as above, and then placed over carbol fuchsin solution, as above described, kept therein for thirty minutes at 37° C., at ordinary temperature for one-half to one hour, then washed in warm water, then washed for five to thirty seconds in a solution of nitric acid of the strength of one part of commercial nitric acid in three to ten parts of water, next washed in water and placed over methyl blue aniline water for half a minute at ordinary temperature, then washed in water, dried, and mounted in balsam: the tubercle bacilli are red, all other corpuscles, cells, nuclei, and septic bacteria are blue. (5) To stain spores in bacilli. Spores do not stain after the ordinary methods so long as they are alive; they refuse to take any dye unless they are previously killed; and therefore in ordinarily stained specimens the bacilli are stained, but the spores remain without colour. The ordinary method of drying does not kill them, and it is accordingly necessary first to overheat the cover-glass specimen sufficiently. This is effected by drawing the cover-glass specimen several times (ten to twenty times) through the gas flame, or by holding it a good way above a small flame for several seconds up to half a minute, till the cover-glass is so hot that touching it with the palm of the hand would produce an unpleasant sensation; but of course the heating must stop short of charring. The specimen is then put on a carbol fuchsin solution and kept there at 37° C. for one half to one hour, or the watch-glass containing the carbol fuchsin solution and the cover-glass specimen is covered with another watch-glass, and is then rapidly heated over a flame till boiling point of the fuchsin is reached; then the specimen is washed in water—sometimes it is necessary to dip it once or twice in alcohol—and placed in methyl blue aniline water for twenty to forty seconds, then washed in water, dried, and mounted in balsam: the bacilli and their threads are blue, the spores, both those in the bacilli as also those that are free, are bright red. The same effect is produced if, instead of carbol fuchsin, a 2 per cent. watery solution of rubin is used, the rubin being heated over the flame till the first bubbles appear, washed in water, then quickly stained in methyl blue. Another method is this: treat the cover-glass specimen as above, i.e. stain in fuchsin, then pass through nitric acid (1 : 10), wash in water, stain in methyl blue, wash in water, dry, and mount; the spores are red, the bacilli blue. The spores appear deeply stained also in specimens stained with one dye only, provided the specimen has been previously well overheated; and in such a case, while the colour can be easily removed from the bacilli either completely or brought down to a faint tint by washing the specimen in alcohol after the staining, the spores retain the colour with great persistency.

Another useful method of staining bacteria in a thin film, i.e. in a cover-glass specimen, is the Warsowa method. This method gives very good results, and shows the bacteria and other tissue elements in their natural shape and size, which occasionally is not the case in the dried cover-glass specimens, e.g. if the film dried is not thin. The method is this: A thin film of the material is spread out on a cover-glass and then immediately placed film downwards on a saturated solution of mercuric chloride, contained in a watch-glass, and kept there for five minutes, next over alcohol for ten minutes, then placed over the stain, film downwards; after it is well and sufficiently stained, it is washed in water, then placed in alcohol for a few minutes, next placed over clove oil for a few seconds, then over xylol, also only for a few seconds; the xylol is drained off with blotting-paper and the cover-glass specimen is mounted in balsam. If the right amount of washing in alcohol is reached, this method yields excellent results, and shows the bacteria and tissue elements more in their natural shape, size, and outline than the Weigert-Koch method of drying: the drawback is that the stain is not easily removed from the tissue ground-work, and that this ground substance, owing to its being coagulated by the mercuric chloride, takes easily the stain. If the film placed on the cover-glass is not thin, it is liable to come off in the mercuric solution and in the alcohol, but if it is applied thin it becomes fixed by the mercuric solution as a thin coagulated opaque layer, which the subsequent washings in the various fluids do not easily remove. (For Löffler's method of first treating cover-glass specimens with ink (tannin and ferrous sulphate) and then staining with aniline water methyl violet, methyl blue, or carbol fuchsin in order to stain the flagella, *see* 'Centralbl. f. Bact. und Parasit.' IV. Bd. No. 8, 9, p. 209.)

The methods of preparing thin sections of tissues and the methods of mounting them for permanent specimens are not subjects to be specially described here, since these are matters which concern the general methods used in normal and pathological histology. It is sufficient to say that any means by which thin sections of a fresh or hardened tissue are obtainable are good: whether this be by a freezing microtome of one kind or another, whether by ice freezing or ether freezing makes no sort of difference. Cathcart's ether freezing microtome or Roy's ether freezing microtome, or the Cambridge microtome for ribbon cutting, answer every purpose. But we should recommend that the hardening of the tissues (always in small bits) be carried out in Müller's fluid or in alcohol, though the former is in many cases preferable. In the former the bits of tissue remain for two to three weeks, then are transferred to methylated spirit 66 per cent., and after a week to pure methylated spirit. What we are here concerned with are the methods of staining the sections. If these are made of fresh tissues, they must be put into salt solution, not water; but if previously hardened, directly into water. In both instances, before being placed into the staining fluid they are transferred to methylated alcohol. In the case of the sections from fresh tissues, this transferring them from the salt solution into alcohol is not without risk of their shrivelling up too much, and for this purpose they ought to be spread out on a section-lifter in the salt solution, and then, before floating them into the alcohol, the salt solution must be removed as much as possible, so that the edges here and there become fixed on the section-lifter; then a few drops of alcohol are dropped on to the section to coagulate and fix, as it were, the elements, so that when finally floated into the alcohol the tendency of the section to shrink is greatly reduced.

For staining of sections the same dyes are used as are mentioned above, and as regards simple staining very little is necessary to add to what has been said on a former page of staining of cover-glass specimens. The sections are floated by means of the section-lifter from the methylated alcohol into the dye and left there, according to the character of the dye, the thickness of the section, and the nature of the bacteria, from ten or thirty minutes to an hour and more: in some cases it is necessary to leave them twenty-four hours. Also here staining at 35°–37° C. is more rapid than at ordinary temperature. Then the sections are washed in water and passed into methylated alcohol; there they remain for some minutes (two to ten) according to the amount of dye that it is required to remove from the section. In the case of carbol methyl blue, methyl blue aniline water, vesuvin, the treatment with alcohol must be carried out more carefully than after staining with gentian violet aniline water, carbol fuchsin. rubin, Humboldt's blue and violet, and methyl violet, since in the former the dye is more easily removed by the alcohol than in the latter. It is therefore advisable when using Spiller's purple, methyl blue, or vesuvin to rather over-stain the sections in the first instance; and when using gentian violet, methyl violet, carbol fuchsin, or Humboldt's blue, to leave the sections in methylated alcohol for a considerable time. From the methylated alcohol the sections are transferred to absolute alcohol for a minute or so in order to completely dehydrate them. This alcohol also removes some of the dye; but if this be not desirable, it is a good plan previously to colour the absolute alcohol with a droplet of the dye. From absolute alcohol the sections are passed through oil of cloves for a few seconds; this has great power to withdraw the stain from the sections, and it is therefore good to stain this previously with a droplet of the dye. Finally, the sections are placed in xylol for a few seconds to fix the dye, and then mounted in balsam.

For double staining of sections the same principles obtain as were mentioned above in connection with the cover-glass specimens. We will here give a few illustrations: (1) Double staining of sections with Weigert's gentian violet and eosin, rubin and methyl blue, Weigert's methyl blue and eosin, carbol fuchsin and methyl blue, such as can be practised with sections through tissues of anthrax, septicæmia, pyæmia, diphtheria, typhoid fever, erysipelas, pneumonia, swine fever and swine erysipelas, fowl cholera and fowl enteritis; the sections are well stained in the first dye, washed in water, then placed in the second dye. This second staining must be carried out very carefully in order not to lose the first dye altogether; then washed in water, methylated alcohol, absolute alcohol, oil of cloves, and xylol. (2) In the case of tubercle or leprosy the sections are stained well in carbol fuchsin, then washed a few seconds in nitric acid (1 : 3 to 1 : 10), then in water, then placed in Weigert's methyl blue or vesuvin, then washed in water, &c.

(3) Gram's Method.—The sections are taken from alcohol and placed in Weigert's gentian violet or methyl blue aniline water, then after being well stained, are passed through alcohol, transferred to a solution of iodide of potassium 2 grammes, water 300 c.c., iodine 1 gramme, wherein they remain one to three minutes, then they are washed in alcohol till apparently almost decolourised; then the sections are transferred to alcoholic solution of eosin for from a few seconds to half a minute, washed in water, passed through alcohol, oil of cloves, and xylol, and mounted in balsam; the bacteria are of a deep blue colour, the tissue is pink. Many bacteria retain the first dye when passed through the iodine solution; others, however, become thereby decolourised; of course in these latter cases the method is useless—as with the typhoid bacilli, cholera spirilla, and others.

(4) Lustgarten's Method for Staining the Syphilis Bacillus in Sections.—Weigert's gentian violet, in which the sections remain twelve to twenty-four hours at ordinary temperature, and two to three hours at 37° C.; wash in alcohol, then pass them for about ten seconds through 7·5 per cent. solution of permanganate of potassium; wash for a moment in dilute solution of sulphurous acid in water, then wash well in water; if not decolourised, repeat the washing in the permanganate and sulphurous acid solution, dehydrate, clarify, and mount finally in balsam. Tubercle bacilli, leprosy bacilli, syphilis bacilli, and the smegma bacilli retain the dye even after the permanganate; other bacteria become thereby decolourised. De Giacomi, Gottstein, Doutrelepont, and Schütz have modified this method by using, instead of the permanganate and sulphurous acid solution, either dilute solution of per-chloride of iron or dilute nitric acid (1 : 15).

(5) Löffler's Method for Glanders Bacillus.—The sections or cover-glass specimens are well stained (from thirty minutes to twenty-four hours) in watery solution of methyl blue (2 per cent.) to which in equal parts liquor potassæ (1 in 10,000) is added, or: 1 c.c. concentrated alcoholic methyl blue solution, 200 c.c. dist. water, two to four drops of a 10 per cent. solution of potassic hydrate; then wash in water acidulated slightly with acetic acid, then pass through alcohol (sections), oil of cloves, and xylol, and mount in Canada balsam. In the case of cover-glass specimens, after washing in acidulated water,

wash in distilled water, then dry and mount in balsam. This method of staining is not only useful for glanders bacilli, but for many other bacteria.

There is sometimes great difficulty in staining the bacteria in sections of hardened tissue, far greater than in the cover-glass specimens, and it is therefore important in some cases to stain in a prolonged way, and to be careful in the subsequent washings with alcohol. In many instances cover-glass specimens, made of the fresh tissue, present no difficulty in easily and rapidly staining the bacteria, while after hardening, the demonstration of the same bacteria seems to be very difficult and only possible after prolonged staining, and the conclusion seems justified that the hardening has some deleterious effect; this, for instance, is the case in swine erysipelas, in typhoid fever, in pneumonia, in fowl enteritis, and in glanders. As a rule sections made of tissues first hardened in Müller's fluid are easier to stain for bacteria than if hardened directly in alcohol. In some cases the difference is very striking, the bacteria in tissues hardened in Müller's fluid being easy to stain (tubercle, swine fever, fowl enteritis, grouse disease), while from alcohol the same cannot by any means be said.

CHAPTER IV

STUDY OF THE BIOLOGICAL CHARACTERS

In the whole range of bacteriological studies there has been no greater advance made within a short space of time than in the introduction by Koch of the methods of cultivating bacteria on solid media. These methods, now universally adopted, mark a definite epoch. Before Koch, bacteria had been studied largely and successfully by a large number of observers, and their nature, morphology, and biology in many cases very accurately determined: we need only mention Pasteur, Davaine, De Bary, von Naegeli, F. Cohn, E. Klebs, Miquel, R. Maddox, Lister, Billroth, Tyndall, W. Roberts, Heiberg, Zopf, Prazmowski, van Tieghem, Fitz, Weigert, and many others. But the results obtained by these observers, although remarkable, and of fundamental importance, cannot—we say it with the greatest deference to the acumen and thoroughness of these observers—for a moment compare with the results achieved by Koch by his exact methods of cultivation of bacteria on solid media and by his and Weigert's method of staining bacteria. More than that, by the introduction of these exact methods of Koch there has suddenly set in a flow of researches and discoveries which, like a snowball in rolling from the top of a snow hill, is constantly increasing in size, and its advent is felt in wider and wider circles. While before Koch bacteria had been chiefly studied when grown in fluid media, and thereby the right path from error only with difficulty avoided, since Koch these studies are comparatively easy and tolerably exact, though even in this it requires care, attention, and a sufficient amount of preliminary knowledge in bacteriology and pathology. There seems to be an idea abroad, and of which one hears only too often and sees its mischievous results continually, that for bacteriological and pathological studies and research all that is required is a platinum needle for inoculation, sterile nutrient gelatine in test-tubes (which can be easily bought by the dozen), a microscope with oil immersion, a microtome for sections (sections can be of course cut by any dexterous assistant), one or two aniline dyes (also easily bought ready made), and a book on bacteriology. Well, this is not bacteriological or pathological study and research any more than the possession of flasks, burettes, test-tubes, and reagents in bottles well labelled, and a balance and a book on chemistry, represent chemical study and research.

In the study of the biological characters of bacteria, the study of the fresh and living bacteria occupies, or ought to occupy, the foremost place; the aspect and characters in the living state, as seen under the microscope in a drop of salt solution or watched in the 'suspended drop,' are the first step. We have already described and spoken of these on a former occasion, as also of their characters in stained specimens. The cultivation and study of bacteria on artificial media is the next step.

Culture Media: A. Broth.—All bacteria with few exceptions grow well in beef broth, neutral or, better, faintly alkaline, also in chicken broth and in pork broth. Great differences are shown by the different bacteria when growing in this medium. As mentioned above, some few do not grow in this medium when kept at temperatures above 25° C., although most species grow more abundantly at temperatures between 35° and 38° C. Most of them produce a uniform turbidity, some quickly-growing ones in twenty-four hours, others later, the amount of turbidity differing, however, considerably; in some it makes the broth thick and uniform, in others the turbidity is slight, and in others the broth contains smaller or larger flaky or floccular granules. In some, after one, two, to three days' growth a pellicle appears on the surface; this pellicle in some cases is a continuous membrane, in others more scaly; in some it is thick and smooth, white or slightly yellow, in others it is folded, white or slightly brown; in some the pellicle is easily broken up on shaking, in others it is tenacious and remains complete; in some it easily falls to the bottom of the fluid, in others it remains floating. Micrococci, bacilli, and spirilla are capable of forming such pellicles. In some the height of growth—i.e. the maximum amount of turbidity of the broth—is reached after a few days, in others not until after ten days to a fortnight. During the growth there appears in most a whitish or greyish or more or less coloured precipitate, which increases in amount; this precipitate is either small in amount or bulky, it is either powdery or in some cases flaky, or again in others tenacious and viscid. In some instances the broth, the height of growth having been reached, clears again; in this also great differences obtain—for in some the clearing up proceeds uniformly and gradually from the surface, in others it proceeds in distinct layers; in some species of bacilli the broth does not clear at all; in some species the broth after a day or two is tolerably limpid, although copious pellicle-formation goes on on the surface (potato bacillus, scurf bacillus, and others). If this pellicle by shaking be brought to the bottom a new pellicle is formed. In some species the broth never becomes turbid, but the growth begins at the bottom of the fluid in the shape of grey nebulous flocculi which gradually increase in bulk—e.g. bacillus anthracis, bacillus filamentosus.

From this it will be seen that the character of the growth in broth is in the case of the different species most varied, and the aspect and progress of the growth in many cases very characteristic.

Broth is best used as beef broth in sterile flasks or test-tubes, plugged with sterile cotton wool; the broth is made neutral or, better still, faintly alkaline. Acidity or strong alkalinity of the broth is injurious to the growth.

Instead of broth there can be used: (*a*) beef infusion; (*b*) one small tin of Brand's essence, or meat extract, 500 c.c. dist. water, peptone (1 per cent.); (*c*) broth with peptone (1 per cent.); (*d*) hydrocele fluid; (*e*) blood serum; (*f*) alkali albumen; (*g*) broth and glycerine (6 per cent.); (*h*) beef broth in test-tubes to which has been added a small piece of boiled white of egg.

For some non-pathogenic bacteria other fluids can be used instead of broth which contain nitrogen only as simple nitrogenous compounds—e.g. tartrate of ammonium, or even carbonate of ammonium, urea, or uric acid—although many non-pathogenic, and all pathogenic bacteria require, as stated above, some kind of albumen. Those albumen-free fluids are principally composed of salts (potassium and calcium salts, phosphates) and tartrate of ammonium—Pasteur's fluid and Cohn's fluid.

Other fluids similar in composition (Meyer's and others) are used according to the special requirements of specific fermentative actions shown by the particular species of bacteria—e.g. nitrifying bacteria, acetic acid-producing bacteria.

B. Nutrient Gelatine.—Gelatine as a medium for the study of the growth of fungi and microbes was first used by Brefeld and by Klebs, but not until Koch showed its immense value was gelatine of peculiar composition universally used and with such signal success. The nutrient gelatine is used in test-tubes (*a*) as beef infusion gelatine peptone, and (*b*) as beef broth gelatine peptone. The gelatine is added to beef infusion or beef broth, as the case may be, besides 1 per cent. of peptone and 1 per cent. of sodium chloride.

Instead of either beef infusion or broth as the solvent medium, there can be used with the same success: (*a*) Brand's essence, one small tin, in 500 c.c. water; or (*b*) meat extract dissolved in water on the same scale.

To the nutrient gelatine special substances can be added as the special cases may require—e.g. grape sugar, lactic sugar, cane sugar, whey.

The writer uses generally beef broth gelatine peptone, or Brand's extract solution, or gelatine peptone, faintly alkaline. The gelatine is used from 2 per cent. to 10 per cent. Two per cent. gelatine mixture sets well and remains solid at 20° C.; gelatine of 10 per cent. remains solid at 22° C. to 23° C., and even a little higher. In the test-tubes the gelatine, if used for stab cultures, is set straight and upright, for surface or streak cultures it is set slanting; for the latter purpose the writer uses special trays made of wood or tin and offering a slanting surface, so that about twenty-four tubes containing the liquefied gelatine are at the same time placed side by side on the tray, and the gelatine, when set, offers the largest surface without being too near the cotton-wool plug.

For studying the growth of bacteria on the surface or in the depth, the liquefied gelatine is set in a sterile watch-glass, or in a flat glass capsule, or on a glass plate, or in a test-tube, or in other vessels; the gelatine is then inoculated with a capillary glass pipette or a platinum wire, previously dipped in the material containing the bacteria, either by a stab, or at a point, or at several points, or in a line or lines, i.e. streak; and if the gelatine is kept covered up, so as to prevent accidental germs entering from the air, the growth of the inoculated bacteria can be easily examined from time to time under a magnifying glass or under a simple microscope. Because development on the solid nutrient gelatine takes place only at, and is limited to, the spot of inoculation, or the spot where a bacterium had been present or deposited, several different species can grow side by side, and their differences be watched; and it is this simple fact which enabled Koch to isolate and keep isolated different species of bacteria growing simultaneously in a limited area. By this means it is not difficult at once to recognise that a particular material with which the gelatine had been inoculated contained several different species of bacteria, while each can then be isolated by sub-cultures separately. This is an advantage which cultures in fluid media do not offer; hence, if originally into a fluid medium several species are introduced, these all multiplying in the fluid, a mixture of the different crops is the result, all intermingled with each other. By using solid media, not only can the growth of individual species be watched and controlled better and with more exactness, but a separation and isolation from an original mixture of the different species composing it can be achieved with facility. The characters presented by the different species when growing on and in nutrient gelatine are most varied, and for many of them very characteristic. We will here give some of these characters. First and foremost is the power that some bacteria (micrococci, bacilli and spirilla) possess of liquefying the nutrient gelatine in the course of their growth and multiplication, while others do not liquefy it. In stab cultures the liquefaction proceeds from the surface or upper part of the stab—i.e. the channel of inoculation—towards the depth and towards the sides, so that the liquefied gelatine occupies and fills as a rule a more or less funnel-shaped space in the gelatine, the broader basis of the funnel being on the surface; as growth and liquefaction proceed the funnel-shaped space becomes cylindrical. In streak cultures the liquefied gelatine flows down to the bottom of the tube, and the gelatine on which the streak growth takes place becomes transformed into a broad and deep groove, the diameter of which depends of course on the rapidity of the growth and the rapidity of the liquefaction. There exist marked differences (*a*) as regards the rapidity of liquefaction independent of the amount of the growth, for some liquefy with great rapidity and early, others only very slowly and not before some days have passed: (*b*) as regards the character of the liquefied gelatine; in some this is perfectly limpid, the growth settling in the depth of the liquefied gelatine (bacillus anthracis, spirillum choleræ), or it remains on the surface as a scum (bacillus filamentosus), or both (bacillus subtilis); in other cases the liquefied gelatine is not clear, but either uniformly turbid (spirillum Finkler, bacillus Jequirity, and some species of staphylococcus liquescens) or it contains granules and flakes (several species of staphylococcus liquescens, bacillus of potato): and (*c*) as regards the density of the liquefied gelatine; in some the liquefied gelatine is thin and fluid (many species of bacillus subtilis, potato bacillus, spirillum of Finkler and cholera, staphylococcus aureus liquescens); in others the liquefied gelatine is like thick syrup and scanty (some species of staphylococci, bacillus fluorescens of veal pie—bacillus of swine erysipelas).

Those species which do not liquefy gelatine, and their number is legion, show likewise marked differences one from another in stab and streak cultures. As to stab culture, the channel of inoculation is after a few days a grey or white or brownish line made up of isolated or more or less confluent droplets, in some very minute, only visible under a lens, in others large enough to be seen with the unaided eye; in some again the channel of inoculation is a uniform broad growth, in others it remains always very thin; in some species the droplets forming the channel of inoculation are white or grey in reflected, and light yellow-brown in transmitted light, while in others they are conspicuously white in reflected, dark brown in transmitted light. Again, the surface of the stab contains no growth, or only very little in the shape of a few superficial minute granules or droplets (e.g. some species of streptococci), or the surface of the stab is covered with a convex, more or less well-defined circular disc or button (bacillus of Friedländer, some species of staphylococcus), and this again is either white or grey or of a pinkish or slightly yellowish colour; or the surface of the stab becomes covered by a flat thin filmy disc, small in some species, rapidly spreading in others, circular or only slightly angular in some, very markedly crenate and serrated in others; in some limited only to the surface of the stab, not larger than one to two millimetres in diameter, in others soon covering the whole surface of the gelatine.

Equally great are the differences in streak culture—i.e. when the growth takes place in a line drawn longitudinally on the surface of the gelatine (set obliquely in a test-tube) by a capillary pipette or platinum wire. First: the rapidity with which the growth appears in this streak differs considerably in the different species; in some after only twenty-four hours the line of inoculation is already marked as a greyish or whitish streak; in others the growth is not noticeable before two to three days. Then the manner and rapidity with which the streak grows in breadth; in some the growth does not spread much in breadth, in others it rapidly broadens into a band; in some the streak is uniform and homogeneous, in others it is uniform but slightly granular, in others, when seen under a glass, it is made up of minute droplets, more or less separate, but in close contact and even confluent; the margin of the streak is either smooth, and more or less straight, in others it is knobbed, serrated, or bent, with numerous shorter or longer filamentous projections. Then as to the colour and aspect of the streak; in some the streak is greyish, in others white, and in others more or less coloured (pinkish, yellowish, golden brown, greenish, vermilion, &c.) in reflected light; in transmitted light the streak is greyish or brownish, uniform in thickness, or thicker in the centre than at the margin, or the reverse; in some the streak is terraced, in others of uniform thickness; in some species the margin shoots out in thin irregular plaques, in others in fan-shaped patches. In some the growth is moist, in others it looks dry; in some species the growth is extremely limited while on the surface but copious in the depth of the gelatine, or *vice versâ*, the former growing much better under access of air, the latter under deficient supply of air—aërobic and anaërobic.

As a useful means for study, and interesting for differentiation, is the method of adding to the nutritive gelatine traces of an aniline dye, sufficient to stain the gelatine—too much aniline dye acts more or less poisonously on the bacteria and prevents their growth. But when certain dyes are added in very minute quantity, a curious result is obtained by the different bacteria when growing in or on such gelatine: while some refuse to grow even when a mere trace of the dye has been added, others grow slightly, and others very well. Amongst the latter the gelatine will be seen in some cases to become gradually decolourised, beginning from the growth and spreading further and further; the growth itself, at first stained, gradually losing also the colour, beginning from the part nearest to the surface. Great differences in the time and manner are shown in these respects by different species of bacteria. The gradual discolouration of the gelatine, beginning at the growth and gradually spreading through the gelatine, indicates that certain diffusible chemical substances pass from the growth into the gelatine.

Then as to the nature and aspect of the gelatine on which the streak grows; in some this gelatine remains perfectly limpid and unaltered, in others it becomes opaque, while in some it becomes gradually coloured greenish or bluish though it remains limpid.

Another useful method is that of Buchner, viz. adding to the gelatine sufficient litmus to stain it; the change of this substance by the growth is an interesting index of the character of the bacteria.

All these are points which in themselves are sometimes small and insignificant, but, occurring with constancy, and taken with the appearances presented by the growth in other media, are reliable distinguishing characters. (*See* the illustrations of stab and streak cultures.)

PLATE CULTIVATIONS

The most significant characters presented by bacteria are those shown by them when growing in plate cultivations. Owing to the fact that when a particular bacterium is planted into (or finds itself at) a particular spot of solidified nutrient gelatine or agar mixture, it forms a circumscribed growth at that spot—viz. a colony—it is possible to separate different species of bacteria from any mixture, care being taken to first distribute by shaking a limited number of the bacteria in a comparatively large amount of liquefied nutrient gelatine or agar, and then to pour this out into, and allow it to set in, a protected glass vessel, plate, or the like. As the material sets, it fixes, as it were, the bacteria (that have been introduced) in isolated fashion, and each of them (being few and far between) by multiplication gives rise to a pure colony, sufficiently separated from others by material not containing any bacteria, and therefore capable of being easily studied during their various phases of growth by the unaided eye or by a lens. Their mode and rapidity of increase, their aspect, colour, outline, &c., can be watched, and from them by inoculation of new media new pure sub-cultures can be established. All one has to do is, then, to introduce a limited number of bacteria (with a capillary pipette or a platinum wire) from a given tissue, blood, or bacterial culture or mixture into a test-tube containing nutrient gelatine (5-8 c.c.), then liquefy this in warm water, then shake the gelatine carefully so as uniformly to distribute the introduced bacteria, and then pour this out on a flat sterile glass dish covered up with a sterile glass plate or glass dish,[1] or to pour it out on sterile glass plates, watch-glasses, or other vessels, provided that the gelatine forms a thin layer; then the gelatine is allowed to rapidly set, by either leaving it to itself in a cool place or by placing the vessel on cold water or ice (according to the temperature of the air). As the colonies make their appearance in the plates in the course of a few days, the plates being kept in the incubator at 19–21° C., if necessary in a moist chamber —e.g. under a glass globe containing moist filter paper—the examination of them can be easily effected under a magnifying lens or with a low power under the microscope. If, however, the material from which the plate cultivation is to be made originally contains large numbers of the same or of different bacteria—e.g. intestinal evacuations, sputum, anthrax blood, bacterial culture fluids, &c.—then the direct inoculation of the gelatine with however small a trace of the material brings forth in the plate too large a number of colonies. In these cases it is necessary first to dilute the material, placing a trace of it into a few cubic centimetres of sterile salt solution or broth; shake this up, and then inoculate from this with a small quantity—with the platinum wire or platinum hook—the tube of nutrient gelatine, which, liquefied and shaken up, is used for the plate cultivations. In order to have a successful plate cultivation the number of colonies in a plate must be limited, the colonies must be sufficiently isolated and, if possible, in a single layer. Of course during all these manipulations accidental contamination with other bacteria (air, unclean instruments, or hands) must be avoided as much as possible, rapid and precise working with sterile apparatus being essential for success. (Agar plates, *see* p. 41.)

Tube-plate Cultivation

Another kind of plate cultivations, yielding very good results, and giving excellent permanent specimens of plate cultivations, is obtained in the following manner. Everyone who has practised the above method (Koch's) of plate cultivations in a laboratory in a large city knows that accidental introductions of air-germs, particularly moulds, &c., cannot be wholly avoided, and therefore many such plates become by-and-by spoiled, apart from those in which liquefying organisms develop—for in this case all plates become useless as plates—as soon as the liquefaction has reached a certain degree. But in the case of non-liquefying bacteria excellent permanent plate cultivations are obtained by spreading out by means of the sterile platinum wire or platinum loop or hook (*Oese*, Germ.) a trace of the material (pure or after dilution as the case may require) over the whole surface of the gelatine or agar, set slantingly with large surface in a test-tube—that is to say, rubbing it over the surface; during this operation the tube is held inverted, is then plugged again with its sterile cotton-wool plug, and placed in the incubator. After a few to several days a limited number of colonies are noticed on the surface of the gelatine or agar, which can be easily studied with a magnifying glass or used for sub-cultures. Such a tube-plate cultivation can be kept uncontaminated and in a perfect state for an indefinite time, provided the gelatine or agar is kept from drying up by covering it with a well-fitting india-rubber cap, or, better, with gutta-percha paper melted to the glass wall of the neck of the test-tube.

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[1] The writer had described and figured this glass dish in 1886, long before Petri, to whom generally this form of plate cultivation is ascribed. (See *Micro-organisms and Disease*, 3rd edition.)

Another mode of plate cultivation is that described by Esmarch, and known as 'roll-plate.' The procedure is here the same as in Koch's method, but after inoculation, liquefaction, and shaking up of the gelatine contained in a test-tube plugged with sterile plug, this gelatine is not poured out on plates, but having been covered with a tight-fitting india-rubber cap is rolled, while holding it horizontally, in cold water, till all the gelatine has well set in a thin layer on the inside of the glass tube. The tube is then wiped on the outside and placed in the incubator. Such a roll-plate retains its character as a plate cultivation intact for an indefinite period provided no liquefying colonies be present. By carefully twisting the plug this can be easily removed and sub-cultures be made from the colonies. The examination with magnifying lens is of course also easily carried out, even under the microscope, the tube being placed horizontally in a sort of cradle across the stage of the single microscope.

From what has been said above it must be evident that plate cultivations are indispensable means of study, since by them not only can the different species be readily and exactly studied, but they can be isolated with precision and pure cultivations from them be obtained; besides, by these plate cultivations the purity or impurity of different materials and cultures, and the nature and number of the different species, can be accurately determined (*see* below).

It must also be obvious that however pure—i.e. containing a single species—a given material or culture in broth or other fluids or in stab or streak culture may appear under the microscope or to the naked eye inspection or to a magnifying lens, there is no guarantee that it is really so unless it can be shown that the colonies derived from it in plate cultivations are all the same as regards rapidity of growth, size, aspect, outline, colour, and general nature. And it follows from this that, with justice, the study by plate cultivation (not only in gelatine but also in other solid media, agar, serum, &c.) is considered one of the most essential steps in the study of bacteria, and unless the bacteria have been isolated by plate cultivation of one kind or another no guarantee can be said to exist as to their purity. (*See* illustrations of plate cultivations.)

Now, the different species of bacteria differ in many ways one from another in plate cultivation: e.g. as regards (1) the rapidity with which the colonies grow in a plate after inoculation; (2) their appearance when first noticed; (3) the rapidity and amount of their increase in a given time; (4) the period at which the colonies reach their maximum development, provided they do not liquefy the gelatine; (5) whether or not the colonies liquefy the gelatine; (6) the manner in which the liquefaction takes place, whether clear or turbid, regularly outlined or irregularly; (7) the outline of the colonies; (8) the breadth and thickness of the colonies; (9) their general aspect, whether grey or white or coloured, moist-looking or dry, homogeneous or granular, uniform in thickness or not; (10) whether they show a difference in their size and in the rapidity with which they grow on the surface and in the depth of the gelatine, for just as in stab and streak cultures, so also in plate cultivations, in many species that are developing on the surface the colonies show much better growth than those developing in the depth of the gelatine, or *vice versâ* (aërobic and anaërobic). If we have to deal with bacteria that do not grow well or not at all on the surface, the surface of the cultivation must be covered up by a new layer of gelatine in order to bring the bacteria, that otherwise would be on the surface, into the depth. For this purpose, after the plate is made and the gelatine well set a thin layer of gelatine just on the point of liquefaction is poured over this and also quickly set. The same holds good, of course, for agar plate cultivations.

As to the use of plate cultivations to determine the presence, character, and number of bacteria present in various materials, such as food-stuffs, water, air, soil, &c., more will be said in detail in a future chapter.

Before leaving plate cultivations we must mention a very simple and very useful method of obtaining cover-glass specimens for staining from plate cultivations, viz. the method of 'impression' preparations (*Klatschpräparate* of the Germans); this consists in taking an impression of the colony or colonies by gently pressing a cover-glass on to the gelatine containing on its surface the colony or colonies, and then simply treating this cover-glass like any other cover-glass specimen—i.e. for drying and staining, or for the bichloride of mercury method and staining. If the colony or colonies be thick, the first impression contains, of course, too thick a film, then the second or third impression will be found more to the purpose. Such 'impression' specimens are very easy to handle and to stain, and give, besides representing a fine view of the bacteria in detail, an excellent representation of the nature and character of the colony as a whole.

Since the nutrient 10 per cent. gelatine does not keep its solid state above 22–23° C. the bacteria cannot be studied and grown in this medium as a solid medium above this temperature, and therefore other media that keep their solidity up to 38° or 39° C., and higher, must be employed. It must be obvious that since certain species of bacteria do not grow appreciably below 25° or 30° C., or do not grow sufficiently quick unless exposed to at least 30° to 35° C., gelatine cannot be used as a solid medium in these cases—e.g. the diplococcus pneumonia, the streptococcus of Schütz in infective pharyngeal abscess of the horse, the glanders bacillus, the tubercle bacillus, the leprosy bacillus, and even some species of bacilli in water. Some species of septic micrococci do not grow in gelatine kept below 22° C.—i.e. in a solid state.

The solid media capable of remaining solid at higher temperature are: (1) nutrient agar, (2) blood serum, (3) potato (Koch); to which may be added (4) bread, (5) paste, (6) soil. The first three are the most important.

(1) Nutrient agar is used in various modifications: (*a*) beef infusion agar peptone, (*b*) beef broth agar peptone, (*c*) Brand's extract agar peptone, (*d*) beef infusion agar peptone glycerine, (*e*) beef broth agar peptone glycerine. In the case of the first three, 1 per cent. agar is substituted for the gelatine in the mixtures mentioned on a former page. Beef infusion or beef broth agar peptone glycerine (Roux and Nocard) is useful for the growth of many microbes which do not grow on ordinary nutrient agar; the two media differ only in this, that 5–7 per cent. glycerine is added to the ordinary nutrient agar mixture.

Blood serum is prepared from sheep's or ox's or horse's blood. The last named is the best, and is used as a solid medium, the solidification being effected after sterilisation (heating for one to two hours at 58–62° C. on four to six successive days) by heating up gradually to 70° C. after Koch's plan and with the apparatus designed by Koch.

'Condensation water'—i.e. a small amount of clear fluid—is always present at the bottom of the test-tubes containing slanting solid agar mixture or slanting solid blood serum; but this water gradually evaporates if the tubes are kept in the incubator.

Potato: best as boiled potato. It is used by cutting with a wide cork borer a long piece from one-half of a potato (this piece has one flat surface, the rest is curved. and the piece is attenuated at one, the upper, end); this piece is put at the bottom of a sterile test-tube on a small cushion of sterile cotton wool, then the test-tube is plugged and sterilised in the steam steriliser. (*See* the illustrations of potato cultures.)

Or the potato can be used as a half, or as a disc, a block, or the like. The writer always now uses potato in test-tubes with a cushion of cotton wool at the bottom of the tube. Such cultures keep for an indefinite time without accidental contamination (moulds) so common in ordinary potato cultures under glass-cover.

Bread and rice paste moistened with broth, and boiled egg, kept in a sterile test-tube. or in a sterile glass capsule or dish, are also used.

Soil in cakes, sterilised, without, or moistened with, broth, either in sterile capsules or in watch-glasses.

It need hardly be added here that other solid materials, like bits of turnip and cucumber, can be sterilised in test-tubes in the steam steriliser and then used as solid media for the cultivation of bacteria. Of course, the disadvantage that all these have is that they are not transparent, and therefore can only be used for studying the general character and nature of the growth on the surface, and then only in reflected light.

Agar mixtures are very useful for plate cultivation of those species that require for their growth higher temperatures than 22° C. Nutrient agar is melted in hot water of about 80° C. or higher, then cooled till it is about 40–45°, at which temperature it still keeps fluid; the inoculation is now made, and the agar shaken and poured out in plates, in which the material almost immediately sets. The condensation water which sometimes appears, particularly if the nutrient agar is of very recent make, is very troublesome ; appearing on the surface of the set agar in the plate, it swamps the surface colonies very soon, and the whole surface of the agar plate soon becomes covered with the growth. In such cases it is useful to keep the glass dish containing the set agar film in an inverted position and slightly raised at one side, and over filter paper previously steeped in perchloride of mercury solution (1 in 500) and dried ; this absorbs the condensation fluid as it runs down the inclined side. But in agar that has been made some time—one or more weeks—this is not necessary.

Isolation of different species of bacteria by fractional cultivation (Klebs) and by dilution (Naegeli and Lister) are also in use, but less so since gelatine plate and agar plate cultivations fulfil all requirements.

CHAPTER V

BIOLOGICAL CHARACTERS OF BACTERIA

In the foregoing chapters we have given the methods of studying bacteria from various sources, and have shown (1) their different characters when examined fresh under the microscope ; (2) their growth and multiplication and eventually spore formation when watched in the 'hollow' object-glass in the 'suspended drop ;' (3) their character in stained films from the original materials or from culture dried and coagulated on cover-glasses ; (4) the character of their growth as colonies in plate cultivations of one kind or another ; (5) their character in stab and streak cultivations on nutrient gelatine, on nutrient agar mixture, on serum, and on potato ; (6) their character in broth cultivations.

All these points have to be considered in order to determine the characters of particular bacteria, and to be able to compare them with, and to distinguish them from, other species. Often it is found that though two or more species are very similar in several of the above points, they show a decided difference in one or the other of these media. For instance, several species of streptococci are very difficult to distinguish if studied in a general way in plate cultivation, on gelatine and in agar, in broth or on serum, but it will be found on careful comparison that the rapidity and aspect under which the colonies appear in the plate cultivations, the progress, rapidity, colours, and outline of the growth on and in gelatine, on agar, and in broth, show slight well-defined differences ; so also with other bacteria—e.g. the bacillus of Friedländer and the bacillus in rhinoscleroma are very similar in and on gelatine and agar, but yet there exist definite though small differences. There exist a number of various species of motile bacilli which have about the same size and general morphological characters, including formation of leptothrix and spores, and which also in plate cultivation, in stab and streak cultures on gelatine, and in broth cultures are very similar; nevertheless there are in these media slight differences that are easily overlooked, but on potato the differences are striking. So also the typhoid bacillus; the writer is acquainted with, and has in his possession, a species of bacillus which was isolated from the mesenteric glands of a child dead of summer diarrhœa, and which it is impossible to distinguish from the typhoid bacillus in gelatine cultures, on agar, and in broth, but on potato the difference is striking. These examples could be easily multiplied.

In studying those species of bacteria which are connected with specific disease, besides the above points to be attended to there is one which ought not to be lost sight of—that is, while demonstrating the existence of the particular species of bacteria by cultivation from the blood or tissues, these bacteria must be demonstrated also by stained cover-glass specimens of the fresh morbid tissues or fresh blood, as the case may be. There may be difficulties in this—as, for instance, if the number of the specific bacteria present in those tissues and blood be too limited for showing them in a small particle of the tissue or a droplet of the blood used for such cover-glass specimens—but such cases are only few; in most instances they can be shown to occur in such specimens, even if sometimes several such specimens may be needed to demonstrate the bacteria. Plate cultivations and stab and streak cultivations yield, as matter of course, much more positive results, even where the number of bacteria appears small in the tissues when examined under the microscope.

Classification.—Owing to the rapid increase and perfection of the methods above described, the number of different species of bacteria already well differentiated has become very great, and it is steadily on the increase. Numbers of species of micrococci, which in former years were all considered as one, have become a whole family of species. We need only refer to staphylococcus and to bacillus subtilis. Staphylococcus is now merely a generic name, and there are a very large number of species of staphylococci known, well differentiated one from another; nay, more, staphylococcus pyogenes was once the name of a species, but it is now well known that this is a group of species. The name of staphylococcus pyogenes aureus is still by many given to one species; but the writer is sure, from definite and systematic observations on this subject, that this name comprises also several species. Streptococcus is another such name, as was mentioned on a former page; it indicates the power of micrococci to form chains; there are a considerable number of different species of micrococci which belong to this group; streptococcus pyogenes of Ogston and Rosenbach, until a few years back, was regarded as a single species of streptococcus, but this also comprises a number of different species. Bacillus subtilis, formerly the name of a species, is really the name of a family of similar species. In choosing the name for any one species there does not, at present, exist an understanding on the part of bacteriologists about any standard character, but a name is chosen by one bacteriologist according to one prominent character, by another according to another; hence there exists a tendency to name the same species by different appellations. This is particularly and strikingly illustrated when one looks through the literature that has accumulated in recent years on water bacteria and other saprophytic bacteria; it is less so in the case of bacteria connected with disease, for in these cases the name is the name of a class, and to it is added the name of the disease with which it is associated—e.g. bacillus choleræ gallinarum, bacillus anthracis, bacillus tuberculosis, bacillus mallei; but occasionally also in these groups one meets with appellations which are most misleading—e.g. bacillus cuniculicida, meaning by this a particular bacillus (formerly called a bacterium) which is fatal to rabbits, and discovered by Koch. As, however, there exist a host of different species of bacilli which are cuniculicida, it would be better to call the former B. cuniculicida Koch, and to distinguish it from other B. cuniculicida. Or take the case of spirillum sputigenum, the name given to spirilla occurring in the fluid of the mouth, it is clear that this is not one but several species, and that when their characters are better studied other names will have to be added.

The best account of this constantly and rapidly growing subject has been published by James Eisenberg, 'Bacteriologische Diagnostik,' 3rd edition, 1891.

HEAT

In a former chapter we have stated the important differences that exist as regards the influence of different temperatures on the different species of bacteria; amongst other points it was mentioned that while in most cases certain higher temperatures (30–38° C.) favour, lower temperatures (16–17° C.) and also too high temperatures (42–45° C.) diminish, the power of multiplication. In some few species—e.g. bacillus thermophilus—extremely high temperatures (65–70° C.) are still appropriate. We further mentioned that in some cases the bacteria do not grow at temperatures above 25° C., while others do not grow at temperatures below 22° C. Now in all cases of the multiplication of bacteria heat is evolved; in those that grow rapidly at ordinary temperatures (16–22° C.), amongst them the typical putrefactive organisms or saprophytes, the amount of heat evolved is considerable and easily noticeable; and there is a fruitful field of research opened in this respect—viz. to ascertain accurately the manner and amount of this heat production in the different species. As we shall point out later, Birch-Hirschfeld has ascertained this evolution of heat also for tubercle bacilli. It has been stated that the febrile rise of temperature in the body in the case of rapidly growing pathogenic bacteria is probably due to such a cause; but this is not based on any direct evidence; on the contrary, it is more probable that where in a disease rise or fall of temperature takes place, it is due to a direct action of the chemical products of the bacteria on the heat-regulating mechanism in the body. Take, for instance, the case of anthrax and some cases of septicæmia; here the rise of temperature is greater in the initial stages of the multiplication than in the later stages when the bacteria have become more numerous—in fact, towards the stages when they have become very numerous the temperature of the body rapidly falls. An apparently opposite result is noticed in the case of the spirilla of relapsing fever and the plasmodia of malarial fever, for here the onset of the fever-rise is coincident with, or even follows the immigration into the blood of the parasites. We say apparently, because there is ample evidence that rise of temperature has not its cause in the blood but in the tissues. But the general observations of artificial cultures of various species of saprophytes, as well as of pathogenic bacteria, prove that under these conditions, and growing at ordinary temperatures, there is often an appreciable rise of temperature noticeable. This rise is obviously the result of oxidation and disintegration processes going on in the nutrient medium in connection with the multiplication of bacteria. The writer has noticed in a general way, as was *à priori* to be expected, that in the case of motile bacilli and motile spirilla this rise is more appreciable, *cæteris paribus*, than in other not motile bacilli; and the same is the case in those species which grow best on the surface of the nutritive gelatine as compared with those that grow better deep in the fluid. On the detrimental influence of higher temperatures *see* the chapter on Disinfection.

LIGHT

Diffused light has a small, direct sunlight has a powerful, inimical influence—both inhibitory and germicidal—on the growth and life of many bacteria.

The observations of Duclaux on this point comprise many species of bacteria, and those of Dr. Downes have added much valuable knowledge to this subject. Dr. Downes finds that the influence of direct sunlight has a very marked germicidal effect on various microbes—e.g. anthrax bacilli, spore-less and spore-bearing, and tubercle bacilli.

But while in many cases the direct sunlight has an inimical influence, there exist certain species of bacteria, which in their growth and development evolve phosphorescent light.

Engelmann studied a species of bacillus (bacillus photometricus) which, owing to its great sensitiveness to light, he used to accurately measure light.

As regards the phosphorescent bacteria, the following observations have been made. It has been known for a long series of years that decomposing wood and decomposing sea fish occasionally become phosphorescent, but Pflüger was the first to show that the phosphorescence in the case of fish was due to the growth thereon of bacteria. Recent researches by Ludwig, Fischer, and particularly Lehmann ('Centralbl. f. Bacterien.-u. Parasitenk.,' V. 24) showed that the phosphorescence of bacillus phoscorescens Fischer is a result of its growth and multiplication under certain conditions, but not under others. This bacterium growing in gelatine, broth, boiled or raw meat or fish, potato, &c., under access of oxygen, produces phosphorescence; when growing in the depth phosphorescence is absent; in CO_2 (Fränkel) the microbe grows but does not show phosphorescence. Whether the phosphorescent condition of the nutritive medium is due to special chemical products, to a mucous capsule, or to the protoplasm of the bacteria is not decided. (*See* also on phosphorescent bacteria, Oscar Katz, 'Centralbl. f. Bact. u. Parasit.,' IX. No. 5.)

For highly interesting observations on infection of various sea animals (invertebrates) in the living state with phosphorescent bacteria, *see* M. Girard, 'Comptes Rendus,' Sept. 23, 1889.

PIGMENT

This is a remarkable and interesting phenomenon exhibited by a great many species of bacteria when growing in one or another medium. While some possess in this respect a highly specialised character, capable of forming a well-defined pigment in most conditions of growth, others assume a pigmented aspect only while growing on one particular medium. Of the former class are those well known since Schröter and Cohn as the 'pigment bacteria'—e.g. bacillus prodigiosus, micrococcus aurantiacus, micrococcus chlorinus, bacillus ruber, bacillus pyocyaneus of green pus, bacillus cyanogenus of blue milk, micrococcus magenta, spirillum rubrum, and many others; to the latter class belong bacteria which only on a particular medium, e.g. on potato, form a pigmented growth, such as bacillus of glanders, spirillum of cholera; or on agar, staphylococcus aureus. With few exceptions (spirillum rubrum) the production of the colouring matter is dependent on free access of air; in the absence of this the colour is not produced, though the microbe shows active growth.

REACTION OF MEDIUM

Most species of bacteria grow best in faintly alkaline media, but there are some species which show good growth in even slightly acid media, and a few show very good growth in acid media of a certain definite chemical character—e.g. certain bacilli found in normal acid urine, and growing in this urine as long as it remains acid. In fact, the increase of acidity in the normal urine during the first twenty-four hours is referred to the fermentative action of these bacilli. Then the various species of bacilli which are concerned in converting sugar into lactic acid (souring of milk) grow well when the medium has become distinctly acid by this reagent; likewise the bacillus aceti, which is concerned in the oxidation of alcohol into acetic acid (e.g. souring of beer, wine) grows well in acid media. On the other hand, many bacteria refuse to grow in even faintly acid media—e.g. the anthrax bacillus, the streptococci, many saprophytic bacilli and micrococci, most of the pathogenic bacteria, micrococci, bacilli, and spirilla—although, as has been mentioned, many of them grow well on potato, which has a slightly acid reaction (malic acid).

The addition of acid to an otherwise favourable medium—e.g. acetic acid, citric acid, various mineral acids, as free acid or as acid salts—converts this medium into an unfavourable soil, and if, before the addition of the acid, growth of one or another species of bacteria had been taking place in that medium, the addition of the acid stops the further growth, and, if added in sufficient amount, kills the bacilli and micrococci—but not the spores—if acting on them for a sufficiently long time. And in this respect it must be mentioned that, though many bacteria themselves as they multiply produce no change in the reaction of the medium, others produce distinct acidity, while others produce only slight acidity and some even alkalinity. A useful method for studying this change going on in a given medium by the growth of bacteria is to add, after Buchner, a small amount of litmus solution; this in itself has no bad effect on the growth, and by the change of its colour, the change of the reaction—if any—brought about by the growth of the bacteria can be easily followed.

Petruschky describes minutely the results of a very large number of observations made on several dozens of different species of bacteria in this respect, and he finds ('Centralblatt f. Bact. u. Parasit.' VII. Bd. Nos. 1 and 2) that some species do not alter the original alkalinity of the medium (whey); of this kind is the bacillus of fowl cholera, bacillus of Koch's septicæmia of mice, and bacillus of rabbits' septicæmia. Others produce a greater or lesser amount of acidity; others produce alkali. In No. 2 of vol. vii. (p. 53) of that journal Petruschky gives a very interesting tabular statement of those species, and of the amount of acidity or alkalinity they are capable of producing when growing in that particular medium.

It is probably to the production of acidity as also of other substances—e.g. phenol—that the growth in certain cultivations ceases before the nutritive value of the medium has become exhausted, and, further, that the microbes (except the spores) remaining in that medium gradually die. Take, for instance, the two species of spirilla known as Koch's cholera spirilla and Finkler's comma bacilli; both species when growing in broth or in nutrient gelatine, which latter becomes liquefied by either of them, produce acidity, slight but distinct, after some days' growth more pronounced in the former, i.e. Koch's spirilla, than in the latter, i.e. Finkler's comma bacilli; and in accordance with this it is seen that the cultures of Koch's spirilla undergo degenerative changes and altogether die much sooner than those of Finkler's comma bacilli. This same phenomenon can be demonstrated also on some species of staphylococci and streptococci and on non-spore-forming bacilli. But not in all species of bacteria in which the gradual dying off, or at any rate the stoppage of further growth, in the culture takes place is this fact due to acidity, for in some no acid is formed and still the microbes gradually die off, or their growth comes to an end even where no exhaustion of the nutritive material had taken place. Thus, for instance, the typhoid bacillus, many species of streptococci, the diphtheria bacillus when growing in streak cultures on nutritive gelatine or other solid media, after some weeks' growth, come to an end, and yet there is no appreciable acidity or exhaustion of the medium produced. The writer has had many plate cultures (on slanting gelatine in tubes, *see* a former page) in which, when a colony, having reached its maximum development, was removed by scraping it off from the gelatine, no new growth took place on this particular spot previously occupied by the colony, although the medium of this spot could not of course be considered as exhausted, and although with the colony so removed any number of sub-cultures can be started without difficulty. Other bacilli that have been examined in this respect behave in the same manner—e.g. several species of streptococci, the Middlesbrough bacillus of pneumonia. In these cases it is then neither acidity produced in, nor exhaustion of, the nutritive gelatine which is the cause of the growth coming to an end, but there must be other substances at work which have been produced by the bacteria, and which substances, though in some cases they do not kill the microbes like those just mentioned, in others kill the microbes themselves, like those previously named—the typhoid bacillus, Koch's and Finkler's spirilla; the nature of these substances is not ascertained.

Many substances which when added to particular bacteria have the power to kill them, or to inhibit their growth when added in minute quantities to a medium otherwise favourable to the growth of these bacteria ; in the former case we speak of the killing power, in the latter of the restraining power, of the substances. We shall speak in detail in a separate chapter of these substances, but at present we only wish to point out that the former action is spoken of as disinfection, the latter as antiseptic action—two totally different things. Of these substances the number is legion ; from the mineral acids like sulphuric and hydrochloric acids, and the coagulating alcohol, to the powerful specific disinfecting action of carbolic acid, iodine, and perchloride of mercury, a large number of substances are known which, according to the strength used, have either a restraining or a disinfecting action.

CHAPTER VI

RELATION OF ANIMAL TISSUES TO BACTERIA

A DIFFERENT influence on bacteria is effected by the living and dead tissues of the animal body. Tissues that are dead but are still connected with the living body furnish for many bacteria a good soil for their growth and multiplication. All those parts which though in immediate contact with normal tissues are nevertheless more or less loosened and unconnected either with the vascular or nervous apparatus must be regarded as practically dead tissues. Thus the more or less detached epithelial surface-layers in the cavity of the mouth, tongue, pharynx, vagina, urethral orifice, and nasal cavity, the mucus attached to the surface of mucous membranes—mouth, pharynx, larynx, trachea, and bronchi—or in the mouths of the ducts of the mucous glands, the mucus and other secretions, and contents of the small and particularly of the large intestine ;—all these represent a good soil for the growth and multiplication of various species of bacteria, since in these materials they find a good proteid nutritive material, and in warm-blooded animals there is the best degree of temperature and moisture present. The detaching epithelial scales and mucus on the surface of the mucous membrane of the mouth, tongue, tonsils, and pharynx, and the fluid in the cavity of the mouth and pharynx, represent the very best conditions, and accordingly we find there constantly the most luxuriant growth of the most varied species of micrococci and bacilli : staphylococcus liquescens and non-liquescens, both sometimes forming continuous masses (fur) on the surface of the papillæ of the tongue; streptococcus, a capsulated bacillus (Sternberg) similar to the bacillus of Friedländer; a leptothrix forming motile bacillus; a leptothrix forming non-motile bacillus, this sometimes in enormous masses on the surface; occasionally a bacillus similar to the Klebs-Löffler diphtheria bacillus (Hoffman): the pseudo-diphtheria bacillus of Löffler; a small bacillus motile and not forming leptothrix; a diplococcus similar to the diplococcus pneumoniæ of Fränkel and Weichselbaum; a fine spirillum, spirillum denticola, particularly in caries of teeth; a comma-bacillus similar to Finkler's comma-bacillus (Miller); a comma-bacillus somewhat smaller than this (Miller, 'Die Microorganismen der Mundhöhle;' Podbielsky, 'The Micro-organisms of the Oral Cavity;' Centralbl. f. Bact. u. Parasit.,' IX. Nos. 18, 19; also Dr. Th. David, 'Les Microbes de la Bouche,' Paris, 1890). Also in the mucus of the nasal cavity various species of micrococci, bacilli, and spirilla are present; in the contents of the lower parts of the small intestine their number is considerable, and in those of the large intestine their number is legion. In the normal mucus of the respiratory system[1] they are also present, and in the mucus and inflammatory products in the pharynx, larynx, less in the bronchial system, their number is sometimes great. There is a very great difference noticeable in this respect between the mucus derived from the bronchial system in the normal and the inflammatory secretions, as in catarrhal and other inflammatory states—since while in the former the number and species of bacteria are comparatively limited, in the bronchial inflammatory states their number is sometimes found extremely great. So also in inflammatory conditions of the fauces—e.g. in tonsillitis and in ulcerations—the number and species are extremely great.

The superficial layers of the epidermis—i.e. the stratum corneum—contain under normal conditions bacteria of different species (Bizzozero, Bordoni Uffreduzzi), which were studied by the latter observer in their morphological and biological characters. In sections through the normal mucous membrane of the alimentary and respiratory organs it is difficult to find any bacteria even in the most superficial layers of the epithelium. In sections through the normal mucous membrane of the mouth, the tongue, fauces, pharynx, larynx, and trachea, particularly the tongue and tonsils, the bacteria attached to or lodged between the most superficial scales of the epithelium are not difficult to demonstrate, and occur chiefly in the form of micrococci and bacilli. They cannot be traced into the middle and deep layers of the epithelium unless there is degeneration or breaking down of the surface, due to inflammation, ulceration, or the like, going on. In these conditions the bacteria can be seen in large numbers attached to these points of broken-down tissue, and from here they extend also into the depth; and it will be noticed that as we pass from the most superficial points of broken-down tissue into the depth towards the inflamed, but not broken down, parts, the number of bacteria gradually diminishes, and as we come to more or less normal parts, they altogether disappear. This would show that these bacteria thrive only where dead or diseased tissue exists, and that the more healthy the tissue the less they are capable of existing. This refers to bacteria of which the representatives are normally present on these surfaces—i.e. bacteria which are true saprophytes—and amongst these micrococci are better able to penetrate than bacilli. As regards the epidermis under normal conditions, no bacteria are found deeper than the surface of the stratum lucidum; in inflammations, ulcerations, and breaking down they can be traced also into the depth according to the amount of breaking down of the tissue. In extensive ulcerative processes in the skin and mucous membranes the number of the bacteria on the surface, and their power of penetration from the surface into the depth, particularly that of micrococci and some small bacilli, goes on on a large scale, often forming continuous streaks and patches, sometimes filling a vessel containing blood in stasis or a lymph space or cleft, or other discontinuities in the tissue. In severe degenerative changes of the mucous membrane of the alimentary canal one sees bacteria covering in continuous masses the surface and extending thence into the depth, particularly into crevices and clefts like those formed by the detachment of the epithelium lining the glandular tubes in the mucous membranes; thus in dysentery, diphtheria, and Asiatic cholera, crowds of bacteria are seen extending in masses into the cavity of the Lieberkühn's follicles, and into clefts left by the detachment of the epithelium lining these glands. And the same may be said for other tissues where inflammatory and ulcerative processes occur in connection with a surface. It has been shown experimentally by Wyssokovitch ('Zeitschrift f. Hygiene,' Bd. I.) that when bacteria are introduced into the normal blood system they disappear without settling anywhere in particular; but if previously some ulcerative or degenerative process had been established, the introduction of saprophytic bacteria into the vascular system is followed by these bacteria becoming carried to and settling in these foci of degeneration, and here they are seen to multiply with great rapidity. Similarly it has been shown that various species of saprophytic bacteria introduced into the vascular system of a normal animal soon disappear altogether, the spleen being the organ to retain them longest; some disappear sooner than others; spores of bacillus subtilis remain for some time in, and are recoverable by cultivation from, the spleen.

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[1] Weibel, Babes, and particularly Besser, on the bacteria present in mucus of the nasal passages.

From all these considerations it follows that the presence of various species of bacteria in various organs in which degenerative, ulcerative, suppurative, and necrotic changes are going on may be of the character of secondary invasion. It is a well-known fact that has been observed over and over again during many years past that such changes in the various organs in connection with, or subsequent to, some infectious and other diseases are in some cases associated with the presence of various bacteria, not having any causal relation to the primary disease, but due to their secondary access to these parts. But also for the normal alimentary canal (the lower ileum) it has been proved by Bizzozero, Ribbert, and Ruffer, that bacteria are capable of penetrating from the surface into the tissue of the mucous membrane; in the perfectly normal Peyer's glands of the cæcum of the rabbit it is not difficult to trace small bacilli from the intact free surface into the lymphatic tissue of the lymph follicles, either as isolated bacilli or enclosed as masses in large cells. The same applies to the tonsils, as shown by Ruffer. How much more will such an invasion be possible if the alimentary canal be in a diseased state, or after death? There is no difficulty in finding various species of bacteria in the portal system of the liver and in the spleen if the *post-mortem* be delayed for some time, say, forty-eight hours or more, notably in warm weather. On the peritoneal or serous surface of the alimentary canal bacteria, chiefly motile bacilli, are sometimes found on *post-mortem* even after a few hours in warm weather; these by their motility and rapid multiplication must have penetrated into the dead mucous membrane, and through this out into the peritoneum. Koch found in a strangulated person bacilli in the vertebral arteries six hours after death. In the large vessels of the inflamed lung and in the tissue around, the writer has seen septic bacilli twelve hours after death. Similarly he has found motile septic bacilli on the capsule of the spleen of mice and guinea-pigs twelve hours after death. In the larger branches of the portal vessels he has met in the summer with micrococci and motile bacilli six hours after death. In necrotic patches of the liver, in the tissue of the tubercular lung, septic micrococci and septic motile bacilli are found in masses, where they must have been present during life.

From all this it follows that while saprophytic bacteria of various kinds are normally present on surfaces and in cavities connected with the free surfaces—i.e. the outer air—they have not the power, unless specific, to thrive in the normal living tissue ; but the tissue becoming diseased, disorganised, or dead, can easily become the seat of growth for bacteria that have invaded the tissue or been carried there. Now the important question arises, What is the cause of this inimical power exerted by the normal living tissues on non-specific bacteria? A large number of observations carried on within the last few years by Fodor, Buchner, Ogata, Sirotinin, Nutall, and particularly Niessen, have shown that the plasmatic fluids of the body—lymph and blood—have in their fresh and living state the power to destroy and kill bacteria brought into contact with them. The experiments of Buchner, Nutall, and Niessen have shown that the fresh blood plasma used in the test-tube has a remarkable power of doing this, although this power differs considerably as regards different species. Thus, micrococcus aquatilis, cholera spirillum, anthrax bacillus, typhoid bacillus, and the bacillus of Friedländer are easily killed after a few minutes (five to twenty minutes), while others, e.g. staphylococcus pyogenes aureus and albus, streptococcus erysipelatos, bacillus of fowl cholera and swine fever, and proteus hominis are only very slightly affected by it ; on proteus vulgaris, bacillus fluorescens liquescens, bacillus aquatilis, and bacillus prodigiosus it has no appreciable effect. But also in the cases where the fresh blood exerts its inimical action, this only takes place if the relative number of bacteria added is limited, for the killing power of a given quantity of fresh blood is limited, so that if the number of bacteria introduced be too large, the killing power of the blood does not extend to all bacteria ; and having been consumed and exhausted in killing a certain number of them, others escape, and these, then, are capable of rapidly multiplying, as in any other medium. The power of the blood to kill certain bacteria rests with the plasma, and it is the same power that also kills the leucocytes. There is a remarkable parallelism between blood plasma and leucocytes on the one hand and blood plasma and bacteria on the other, for when the blood plasma kills the leucocytes it also kills bacteria, i.e. when the blood and blood plasma are fresh ; fresh peptonised blood and peptonised plasma, on the other hand, kill neither the bacteria nor the leucocytes. When blood is heated to 52° or 58° C. for twenty to thirty minutes (Nutall) it loses the power of killing bacteria, which it otherwise killed ; blood mixed with magnesium sulphate loses the killing power ; when blood is kept for several hours it also loses this power. Blood to which bacteria had been added and thereby killed, coagulates quicker (Grohmann), just as blood which kills the leucocytes coagulates quicker.

Buchner (' Centralbl. f. Bact. und Parasit.,' VI.) has made very extensive observations on the germicidal power of blood plasma and blood serum ; he points out an important antagonistic action vested in these fluids, on the one hand, as to their power of being *nutritive*, and on the other, as to being *germicidal* ; the first depends on materials no longer living, e.g. dissolved or broken-down blood corpuscles, the latter on the ' living ' or ' active ' condition of albumen. Buchner shows that the circulating blood possesses the germicidal property in a higher degree than blood after removal from the body : evidently the former contains in a much smaller degree the particular nutritive elements than the latter, which of course contains the products of the dead or broken-down blood-corpuscles. Buchner further shows that the germicidal power of the blood is not dependent on the leucocytes at all—an important fact, since Metschnikoff and others attribute this function solely to the white corpuscles—and further that it depends entirely on the albumen present in the plasma or serum, as long as this is in combination with salt, or, as he terms it, is in an 'active' state. Plasma or serum free of cells acts germicidally; if from it, by dialysis, the salt is removed, it loses its germicidal power; the salts of the plasma or serum themselves possess, however, no germicidal power. Lubarsch ('Fortschritte d. Medizin,' Bd. VIII. No. 17) thinks it probable that the germicidal action and inhibitive power of the living tissues may in a large measure depend on the chemical activity of the tissue cells, that is, on chemical substances excreted or produced by the cells; hence the battle against bacteria is essentially of a bio-chemical nature, as has been ably demonstrated by Petruschki in a series of papers. It is, however, not decided of what exact nature this chemical substance is; it remains to be shown whether, as Hankin maintains ('Br. Med. Jour.,' 1890), it is a cell globulin, or whether it is a ferment, as is maintained by Ogata ('Centralbl. f. Bact. und Parasit.,' Bd. IX. Nos. 18 and 19).

Sanarelli ('Centralbl. f. Bact. und Parasit.,' Bd. IX. No. 14) gives an excellent *résumé* of the literature of this important subject; he at the same time describes carefully conducted experiments in which he proves the germicidal action of the living pure cell-free lymph of the frog on bacillus anthracis.

It follows, then, from these observations that the killing power of fresh blood on bacteria (strong for some bacteria, slight for others, and wanting altogether for still others) is a power which resides in the plasma, that it is a power which is exhaustible according to the number of bacteria introduced, and that also in some of the positive cases it is lost after the death of the blood, after heating, or after the addition of certain chemical substances.

Phagocytes and Immunity

It has been maintained by Metschnikoff that the power of the living tissues of an insusceptible animal to kill certain bacteria, e.g. bacillus anthracis in the frog, rests with the white blood corpuscles, that these accumulate at the place into which the bacteria have been introduced, and here take up—'eat up'—the bacteria and destroy them, hence he called the leucocytes 'phagocytes.' [For the literature and history of phagocytosis, *see* Lubarsch, 'Centr. f. Bact. und Parasit.,' Bd. VI. No. 20.] Normal frogs are insusceptible to anthrax infection: Metschnikoff introduced bacilli anthracis into their dorsal lymph-sac, and herein noticed that after some time the bacilli are taken up by leucocytes and destroyed; hence in this case the immunity of frogs to anthrax was explained by saying that leucocytes—phagocytes—acting as scavengers, eat up and destroy the bacilli. This theory was then extended by Metschnikoff and others to all cases of immunity and insusceptibility, inasmuch as it was maintained that in all cases of insusceptibility the leucocytes or phagocytes, as soon as the bacteria are introduced, give battle to the bacteria, and by eating them up and destroying them, do away with their potential virulent activity. Susceptibility was explained to mean that the leucocytes do not act as phagocytes, they cannot overcome the bacteria, and therefore the latter, being victorious, multiply and produce infection. Immunity against a second attack was explained by the same theory; that by the first attack the leucocytes have acquired a certain germicidal power, not possessed before, viz. to take up and kill the bacteria, while non-immunity against a second attack was due to the leucocytes not having acquired this power. This 'mechanical' theory of phagocytes was, however, soon subjected to severe criticism.

There is no doubt about the fundamental fact that leucocytes can act as phagocytes, that is to say, no one doubts that the amœboid corpuscles of the blood, and of the lymphatic and connective tissues, do take up into their interior various kinds of formed matter: granules, organic and inorganic, blood-corpuscles or fragments of blood-corpuscles, and therefore there is no *a priori* reason why they should not take up bacteria or other microbes with which they are brought in contact. But this is not what the theory of phagocytosis teaches; for this theory maintains that the leucocytes are the aggressors; that they take up and destroy the living specific bacteria, thereby protecting the animal against infection.

Although Metschnikoff himself has recently somewhat altered the theory by admitting that not only the leucocytes but also the lymph and blood-plasma *per se* are capable of destroying the microbes, yet there is still left the fundamental assertion that the leucocytes of the tissues of an animal insusceptible to a particular disease do destroy the particular microbes, and are the principal instruments of procuring this immunity. Against this various objections have been raised.

In the first place it has been shown that after injection of anthrax bacilli into the lymph-sac of the normal frog, degeneration and death of many bacilli take place, which are free in the lymph and not included in the leucocytes (Fischel, 'Fortschritte der Med.,' IX. 2); that the cell-free, living lymph of the lymph-sac of the frog possesses germicidal action has been mentioned already above (Sanarelli). In the second place it has been shown by Petruschky, and also by Fischel, that long before any appreciable phagocytosis occurs in the frog's lymph-sac, there are already present in the lymph degenerating and dead bacilli, and that not before three hours after the injection of anthrax into the lymph-sac are there the first indications of commencing phagocytosis, viz. bacilli are seen adhering to the surface of leucocytes, but not yet enclosed in their substance.

Thirdly, it can be shown that long before any appreciable leucocytosis occurs in the lymph-sac, and before any bacilli are found enclosed within the leucocytes, numerous microbes are absorbed into the blood circulation, and can be demonstrated in a living condition in the blood and in the spleen. On injecting 5 minims of a salt mixture of anthrax bacilli or of bacillus prodigiosus into the dorsal lymph-sac of a normal frog, and testing the blood of the heart and the spleen by cultivation, ten minutes, half an hour, one hour, and two hours afterwards, innumerable colonies of these microbes are obtained, thus proving conclusively that they are absorbed into the general circulation, and the process of the destruction of the anthrax bacilli, and the immunity of the frog against anthrax, cannot depend on leucocytosis and phagocytosis going on in the dorsal lymph-sac, i.e. at the seat of inoculation.

A further set of objections was raised by Baumgarten, Flügge, and others to the effect that phagocytes, i.e. cells which include the bacteria, are found in many acute and chronic infectious diseases, where they—the phagocytes—are not required, where they can be of no use as regards destruction of the bacteria and the production of protection, for the simple reason that in these cases no protection is ever produced. Thus in mouse-septicæmia of Koch the white blood corpuscles become crowded with the specific bacilli and gradually become disintegrated, and hereby the bacilli, active and virulent, become liberated. In Koch's Egyptian ophthalmia, and in gonorrhœa, the leucocytes are the special nidus for the specific microbes; in pigeons dead of swine erysipelas the leucocytes in the vessels of the liver are crowded with the specific bacilli, and are destroyed by them. In leprosy the bacilli select with pre-eminence leucocytes and round cells: in fact, a leprous nodule is an aggregation of round cells, small and large, crowded with the living leprosy bacilli, and by disintegration of the cells the bacilli become free; in tuberculosis the tubercle bacilli are found in cells, small and large, and that is how the bacilli multiply and the cells become disintegrated. It is true that in the typical giant cells, e.g. in bovine tubercle, the bacilli present in them are most numerous at first, and gradually disappear from the giant cells (Koch), but this is probably due to the necrotic change of the cells themselves (Weigert, Koch), but in many instances we see the tubercle bacilli in leucocytes and round cells of all sizes destroying the cells themselves.

On the other hand, it has been urged that where one might expect that phagocytes should be present, as at the seat of inoculation in an animal possessed of immunity, the phagocytes are either absent altogether or are not present in commensurate numbers. Thus instances have been mentioned where after injecting into an insusceptible animal a dose of the microbes—such as would cause a general fatal infection in a susceptible animal—no phagocytosis, or none to speak of, could be demonstrated. Dogs, cats, and rats are insusceptible to anthrax, yet on injecting a good dose of anthrax material into the subcutaneous tissue of these animals no phagocytosis of an appreciable degree occurs. Fowl enteritis is not virulent for pigeons: on inoculating these animals with a large dose of the living bacilli of fowl enteritis, no phagocytosis occurs at the seat of inoculation. In some other cases, however, of inoculating insusceptible animals with the specific microbes, leucocytosis and phagocytosis do take place at the seat of inoculation.

Thus in symptomatic charbon, to which the rabbit possesses a certain amount of insusceptibility, on inoculating the virus subcutaneously, distinct leucocytosis and phagocytosis are observed (Ruffer); the same is the case with the bacillus pyocyaneus in the guinea-pig, whereas inoculation into the rabbit leads to acute general infection without leucocytosis at the seat of inoculation. The inoculation in the guinea-pig produces the opposite result (Charrin).

The virulent bacillus of diphtheria inoculated into the groin of the guinea-pig produces œdematous swelling, hæmorrhage, and necrosis at the seat of inoculation, and the animal dies; but if the culture is attenuated the injection produces local leucocytosis. The injection of the bacillus of grouse disease in sufficient doses produces in the guinea-pig acute and fatal infection, but it produces no local leucocytosis, whereas if a small dose be used, or if the microbe be attenuated, a distinct local leucocytosis, but no general acute infection, takes place.

On the other hand, in tuberculosis after subcutaneous inoculation with the tubercular virus into the guinea-pig the local leucocytosis is the first change in the course of the general infection: the local suppuration of the lymph-glands at the seat of inoculation being the first step in the whole chain of the inflammation (leucocytosis) and suppuration of the lymphatic glands, the lungs, and abdominal viscera.

We see from all this that while in some cases the introduction of certain specific bacteria into an insusceptible animal produces a local leucocytosis and phagocytosis, in other cases of insusceptible animals it does not produce this, and further that in some cases of acute and chronic infections distinct phagocytosis is observed in animals susceptible to the particular microbe.

Petruschky showed ('Dissertation,' Königsberg, 1888) that even in the frog infection with anthrax can be produced after introducing the bacilli anthracis into the dorsal lymph-sac, and keeping the frog at a higher temperature (30° to 35° C.); under these conditions the bacilli are not killed by the lymph in the lymph-sac or by the leucocytes, and can multiply and produce infection, which they could not do at the ordinary temperature at which the lymph of the frog has the power to destroy the bacilli. Von Emmerich showed that if broth culture of the bacillus of swine erysipelas be injected in considerable quantities subcutaneously into a rabbit which had been some time previously rendered refractory against infection (by injection of culture direct into the blood-vessel), such subcutaneous injection produces no further infection; innumerable masses of bacilli had been thus injected under the skin, and after twenty minutes or so, though they are still to be found at the place of inoculation, they are all dead, no sub-cultures can be established with them; and there is a total absence here of all phagocytosis. The bacilli are here killed, not by the cells, but by something else present in the tissue. Interpreted in the light of the above observations we are quite justified in saying that it is the tissue juice (lymph or plasma) which had produced this effect, i.e. had killed the bacilli.

Dr. Coxwell and the writer have found that while the normal Rana temporaria possesses insusceptibility against anthrax, it succumbs to anthrax (bacilli are found in the blood and spleen) if the frog is, either at the time of the anthrax infection, or shortly before or shortly after, subjected to chloroform-ether narcosis. The lymph-cells after the animal recovers from the narcosis, i.e. after a few minutes, as also the lymph-cells taken from the animal while under narcosis, show normal amœboid movement; the abolition of the insusceptibility of the normal frog against anthrax by chloroform-ether narcosis cannot therefore depend on the lymph-cells themselves, but must be due to some chemical change induced by the narcosis. The same results were obtained in rats. White rats are insusceptible to anthrax, but become susceptible when chloroformed; the narcosis with chloroform-ether lasting about one and a half to two minutes is sufficient to render them susceptible to fatal anthrax. The narcosis is made either previously to or immediately after infection with anthrax; the injection of the anthrax bacilli or spores a few hours after narcosis does not lead to fatal infection. In the positive cases death from anthrax takes place in three to five days, and the blood and spleen contain very numerous anthrax bacilli.

It is probable, then, that whenever bacteria, introduced into the blood or tissues, are unable to multiply there and to produce infection (as in the case of saprophytic bacteria, or in the case of insusceptibility of a particular animal against a particular specific microbe), this inhibition is brought about in the first place by the living and normal blood plasma or the lymph present in all tissues; that this inhibitory power is exhaustible according to the number of the bacteria; thus while in some particular instances (they are tolerably numerous, as will be shown later) infection cannot be produced by small doses, it can be produced by large doses; further, that this inhibitory power varies with the various species of bacteria and with the different animals.

The next question is as to the nature of these germicidal substances. As mentioned on a previous page, Buchner has given good reasons for regarding them as belonging to the albuminous bodies of the lymph and plasma, and he calls them 'alexines' (ἀλέξειν, protecting). It must, however, be clear that whatever the nature of these alexines, they cannot be the same, either in all animals or for the different pathogenic bacteria. The alexines against anthrax in an insusceptible animal, e.g. rat, frog, cannot be the same as the alexines in glanders in an almost insusceptible animal, as the tame mouse. Nor can the alexines which are present in the tissues, and which act germicidally on saprophytic bacteria, be the same as the alexines protective in insusceptible animals against specific bacteria. Again, the alexines protecting a naturally insusceptible animal against a specific microbe cannot be the same as the substances protecting against a second infection a susceptible animal which has passed through one mild attack; that is to say, the natural immunity of an individual cannot be due to the same kind of protective substance as the acquired immunity.

In order to understand the argument it is necessary to mention certain important observations first made by Pfeffer on the remarkable power possessed by different chemical substances towards bacteria and other micro-organisms, substances which either attract or repel bacteria, these phenomena being spoken of as chemiotaxis; the former as positive, the latter as negative chemiotaxis. Pfeffer (‘Unters. a.d. bot. Inst. Tübingen,’ 1887, p. 582) found that motile organisms (bacteria, flagellata, and volvocinea) are stimulated by many organic and inorganic substances in solution-positive chemiotaxis. To mention only a few of the substances: the salts of potassium have a great ‘stimulating’ power, likewise peptone, glycerine, and morphine. Alcohol, free acids, and free alkalies have a negative chemiotactic action i.e. repel the microbes. Ali Cohen (‘Centr. f. Bact. und Parasit.,’ VIII. 6) made systematic observation on this same subject with various kinds of bacteria.

Gabritschevsky, Massart, and Bordet (‘Annales de l'Institut Pasteur,’ 1891, IV. 6), and others tested the action of bacteria on leucocytes, introducing chemical substances in capillary glass tubes into the living body of animals, and then examining these capillary tubes and seeing whether they attracted leucocytes or not; in this way they found that chemical substances either attract or do not attract leucocytes. Thus, for instance, Massart and Bordet found the lactic acid acting powerfully negative chemiotactic; Buchner found collagen, alkali albumen, gluten, and casein acting powerfully positive chemiotactic. Now, Buchner argues, and it seems with justice (‘Centralbl. f. Bact. und Parasit.,’ X. 22 and 23), that when in an insusceptible animal leucocytosis does occur at the seat of inoculation, this leucocytosis is not an expression of the commencing battle between the microbes and the leucocytes, as is maintained by Metschnikoff and his followers, but is due to a positive chemiotactic action on the part of the bacteria (dead or alive), by which the leucocytes are attracted. Extensive leucocytosis (suppuration) has been shown by Koch to occur after injection of tuberculin containing the products of the tubercle bacilli previously killed; suppuration (miliary abscesses) has been produced by Prudden and Hodenpil in the rabbit after injection into the vascular system of the substance of the tubercle bacilli, previously sterilised; also the insertion of sterilised tubercle culture by means of capillary glass tubes into the subcutaneous tissue of the rabbit proves positive chemiotactic action of the dead bacilli towards leucocytes. This chemiotaxis is brought about by the substance—protein—derived from the bacteria themselves, and is dependent on the inimical action of the tissue juices on the bacteria. Where the tissue juices possess this action the bacteria are thereby weakened or destroyed, and only under this condition does their substance—protein—become available to attract the leucocytes; in such cases the weakened and also the killed bacteria are easily taken up by the leucocytes, and these then help to remove them. Under this theory the local phagocytosis observed in insusceptible animals is therefore dependent on the preceding inimical action of the tissue juices on the bacteria. But in the case of a susceptible animal, that is, when the introduction of the bacteria produces general infection and no local leucocytosis at the seat of inoculation, the bacteria, because they remain vigorous, and because they withstand the action of the tissue juices, do not yield the chemiotactic substance—protein —and therefore no leucocytes are attracted to the seat of the inoculation.

In connection with the phenomena of chemiotaxis it ought to be borne in mind that just as certain bacteria exert an attraction on the leucocytes, so also is it imaginable that the cells and tissues exert chemical attraction on certain bacteria, just as in the case of Pfeffer's experiments. This at any rate offers a ready explanation of the conspicuous attraction that one or the other tissue seems to exert towards certain specific microbes. It is well known that in the acute exanthemata, the skin is the tissue which pre-eminently exerts such a positive chemiotaxis on the specific microbes. In anthrax, in typhoid fever, in malaria, and in relapsing fever, the spleen has a conspicuous attractiveness for the microbes ; in tuberculosis it is the lymphatic tissues and the spleen. In this disease the lymph-cells seem to be the particular nidus for the growth and multiplication of the bacilli. It is quite possible that the presence of saprophytes in the lymph-cells of the superficial parts of the tonsils, pharynx, and Peyer's glands (Bizzozero, Ribbert, Ruffer), mentioned on a former page, is to be explained in this way, viz. that these cells possess a chemiotactic action, being a more favourable nidus than the tissue juice, which has a germicidal action.

We have from the foregoing arrived at the conclusion, which seems on the whole the most feasible one, that the principal and essential agent in preventing the growth and multiplication of particular specific microbes within the insusceptible animal is the inimical action of the lymph and blood plasma, the alexines ; this action may or may not produce phagocytosis. In the former case the phagocytosis may help to remove the weakened or dead bacteria, but this is not an essential or necessary factor in the process of the weakening and destruction of the microbes. Where the blood or the tissue juices do not possess this power, the animal is susceptible.

The question now arising is this, Is the acquired immunity due to the same physiological conditions as the natural immunity ? Take, for instance, the case above quoted of Von Emmerich's experiments : a rabbit inoculated subcutaneously with a small quantity of culture of the bacillus of swine erysipelas becomes affected with the disease and generally succumbs to it ; here, then, the juices of the connective tissue have no power to kill or to inhibit the growth of the bacilli. The disease—swine erysipelas—with which such a rabbit becomes affected after subcutaneous inoculation is a blood disease, the vessels in all the organs contain the bacilli, and every drop of blood is capable of producing infection. But if a normal rabbit be inoculated with the bacilli directly into the circulation, although disease follows, it is only of a mild type and the animal recovers. Such an animal is then found to possess immunity against a second infection with these bacilli ; for, as Emmerich shows, injection of large quantities of the bacilli into the subcutaneous tissue produces no result, and the bacilli are found killed at the place of inoculation after twenty minutes. Therefore, by the first attack, something must have happened to the blood plasma and of necessity also to the tissue juices, since these are derived from the blood plasma ; the most feasible view seems to be that something not previously present in the plasma has been added to it by the activity of the bacilli during the first attack. This theory would then be in harmony with the 'antidote theory' of Klebs, by which is meant that the bacilli during a first attack add a product of their own to, or produce a specific chemical change in, the tissue juices and blood which is antagonistic to themselves. And as long as this obtains in the blood and tissue juices the animal retains immunity against the same kind of bacilli. This view would be also in harmony with the fact that, although an animal has acquired by a first attack of one disease immunity against a second attack of this disease, it has no immunity against any other infectious disease. It would be in harmony with this, because since one species of bacilli produces a totally different disease from another, so also the products of one species, or the chemical changes induced, must be of a different character from those of another species; and if therefore a certain substance is added to the blood and tissues by one species, which substance is an antidote to the development of a second crop of the same bacilli—i.e. a second infection—this substance need not be an antidote to another species.

The fact that in a particular infectious disease not leading to death the multiplication of the specific microbes ceases, that is to say, the disease has reached its acme, and the microbes not eliminated from the body are destroyed, is in harmony with the above theory. In the first place, when the multiplication of the microbes has reached its acme, this is not due to an exhaustion (as was once thought in analogy to what takes place in alcoholic fermentation by yeast, i.e. the yeast multiplies in a particular sugar-solution, till this sugar is exhausted and is all converted into alcohol), for the simple reason that the tissues of an animal in the above case are far from exhausted as regards the particular microbe. There is nothing easier than to show that the blood and tissues of such an animal which, while alive, have served for the multiplication of the microbe, when used as artificial media—i.e. after death—are excellent soils for the multiplication of the particular microbe. On the other hand, we have given on a former page reasons which lead us to assume that the arrest in the process of multiplication and ultimate death of the microbe in artificial media is brought about by chemical substances produced by the microbes themselves, that is to say, formed by the microbes in the culture medium, and when this substance (or substances) has reached a certain amount the further progress of the microbe is inhibited and in many cases the microbes themselves are gradually killed off. And it is this same cause which we assume to obtain in the living animal body, in which the multiplication of the specific microbes ultimately reaches its end, i.e. the disease reaches its crisis, and the microbes are gradually killed off and the animal completely recovers. In accordance with this, as long as this antidote remains in the body, the animal is insusceptible to a new infection; but when this antidote in the course of time is eliminated, used up, and altered, the immunity wears off, and the animal is again susceptible to a new attack.

A further support to this theory is given by the recent researches on the behaviour of the animal body to the chemical products of specific microbes. Various observations have been recorded, by which in several infectious diseases the injection into an animal of certain chemical substances, the *toxins*, produced by definite specific microbes in artificial cultures, gives to such an animal immunity against a virulent attack. Wooldridge, Sirotinin, Beumer and Peiper, Salmon, Roux and Chamberland, Löwenthal, Roux and Yersin, and others have proved this. Wooldridge has shown that in a particular form of guinea-pig's septicæmia the injection of the culture fluid, from which the bacilli have first been killed off by heat, gives complete protection against an infection with the virulent bacilli. Wooldridge has further shown that if a particular albuminous fluid in which the bacillus anthracis has been growing, and after the removal of the bacilli, be injected into the rabbit in sufficient quantity, a complete protection is produced against virulent anthrax. Sirotinin, Beumer and Peiper have shown that when Gaffky's (or the typhoid) bacillus is grown for some days in broth, and this broth, after the removal of the bacilli, is injected into mice, no further infection of such animals with the living bacilli, even in large doses, can be produced. (It ought to be mentioned that these bacilli injected in a sufficient dose into mice produce a fatal septicæmia.) Salmon has shown the same to hold good for swine fever; Roux and Chamberland, Löwenthal, and others have shown it for some forms of septicæmia; Roux and Yersin for the disease produced in guinea-pigs by the bacillus of diphtheria. In all these cases it is necessary to inject a sufficient quantity of the culture fluid free of the bacteria, or smaller quantities repeatedly, in order to produce protection against a second infection. The protective inoculation of Pasteur against rabies is based on the same principle. Again, if the quantity of the chemical products, the toxins, be too large, death may be produced in the same way as the bacilli growing in the body produce death by too much of their products; if the quantity be too small, not sufficient of the toxins has been added to the tissues to be protective, but if the quantity is of sufficient amount protection is produced. It seems, then, that the theory of acquired immunity as above stated is in complete harmony with these various facts, viz. that the microbes produce by their growth and multiplication in the tissues certain toxins, which, while present in the blood and tissues, furnish these with the power to inhibit and kill the same species of microbes on being reintroduced a second time—a power not previously possessed by the blood and tissues; further, that as long as these antitoxic substances remain in the tissues, the body remains insusceptible.

The observations of Ogata and Jasuhara ('Mitth. aus d. hyg. Inst. Tokio') and of Hankin ('Centr. f. Bact. und Parasit.' IX.) show that on injecting into an animal (mouse) susceptible to anthrax a sufficient quantity of the blood (Ogata) or of spleen substance (Hankin) of an insusceptible animal, the previously susceptible animal becomes protected, or if already infected the disease becomes arrested. In these experiments the protective alexines present in the naturally insusceptible animal are added to the blood and tissues of the otherwise susceptible animal, and so the blood of this latter is rendered unsuitable for the growth of the anthrax bacilli. This kind of acquired immunity can hardly be the same as the immunity produced by a first attack, or by the injection of the products of the specific bacteria formed in the blood or in the artificial cultures. Besides the experiments above quoted of Wooldridge, Roux and Yersin, and others, the experiments also of Behring and Kitisato on tetanus ('Deutsche med. Woch.' 1890, No. 49), prove this. In these experiments the blood of a rabbit previously made refractory against fatal tetanus is injected into a mouse, which is notoriously susceptible to tetanus; by this injection the latter animal becomes refractory to tetanus. Tizzoni and Cattani prepare certain albumens from the blood of a dog, previously made refractory against fatal tetanus; these substances are injected into an animal susceptible to or already infected with tetanus; by this injection the latter animal is rendered refractory to tetanus, or the development of fatal tetanus is prevented. Moreover, by such injection they have actually cured tetanus in the human subject ('Centralbl. f. Bact. und Parasit.,' X. 24). In these experiments, then, the antagonistic and inhibitory action against the specific bacteria is produced by adding to the blood and tissues of the susceptible animal certain substances which are not the same as the alexines present in the naturally insusceptible tissues, but include the products of the specific bacteria themselves.

In acquired immunity a distinction must therefore be drawn between a refractory state produced by adding to the blood and tissues of a susceptible animal the natural alexines of an insusceptible animal, or certain germicidal or germ-inhibiting drugs (e.g. trichloride of iodine in diphtheria used by Behring), on the one hand, and a refractory state caused by the addition of the chemical products of the bacteria themselves to the blood of the susceptible animal on the other hand.

CHAPTER VII

ANTAGONISM AMONGST BACTERIA

That the chemical products of some species of microbes, while acting inimically on the further multiplication of this species, are not inimical to that of another species has been proved by various observations, but it has also been proved that an inimical action is undoubtedly exerted by the growth of particular species on that of others. It is well known that a number of species of bacteria can exist and thrive under conditions under which other bacteria cannot so exist; take, for instance, the water bacteria, i.e. the bacteria inhabiting common drinking water; these are capable of living and of multiplying on the very small amount of nutritive material present in ordinary drinking water, nay, micrococcus aquatilis and bacillus erythrosporus (Flügge) and others, as mentioned above, multiply even in distilled water (Meade Bolton, Niessen, Percy Frankland); whereas numerous species of bacteria not habitually in water cannot do so under the same conditions; therefore the water bacteria will persist and even multiply, whereas others added to the water, or accidentally finding entrance into the water, will perish, some sooner, some later. Numerous observations have been put on record by Meade Bolton, Wolffhügel and Riedel to show in what way and to what extent various bacteria—the bacillus anthracis, cholera spirilla, the typhoid bacillus, micrococcus tetragonus, and staphylococcus aureus gradually die off when kept in ordinary drinking water, i.e. water very poor in nutritive materials. (The results of Meade Bolton are published in the 'Zeitschrift für Hygiene,' I. 1, p. 76; those of Wolffhügel and Riedel in the 'Mittheil. aus dem k. Gesundheitsamte,' Berlin, I. p. 455.)

It need hardly be said that if nutritive material be added to water, these bacteria will have a better chance of survival and of multiplication, and this chance will be proportionate to the amount of nutritive material added. Similarly De Giaxa ('Zeitschrift f. Hygiene,' VI. 2, p. 162) made observations with reference to the conditions of existence of various bacteria in sea water, and his results are parallel to those made on ordinary drinking water. It need not be specially insisted on that neither ordinary nor sea water in themselves have any killing power on bacteria, but that where such an inhibitory power is observed it is due to the want of sufficient nutritive material, and that the greater the dependence of bacteria on organic material, and the poorer the water in such material, the more unfavourable is such water for the existence and multiplication of those bacterial species.

Next we have to consider the relations between two or more species simultaneously present in the same medium with sufficient nutritive material. Here more rapid multiplication will naturally depend, *cæteris paribus*, on the greater assimilative power; the greater this is, the more predominating will the species become. Thus, for instance, if in any organic material, say dead animal tissues, saprophytic bacteria are present together with bacillus anthracis, this latter has not much chance of growing and multiplying; and hence in any part of an animal dead of anthrax, at first full of the bacillus anthracis, as soon as putrefaction has actively set in, the anthrax bacilli will be gradually killed off by the saprophytes, so that such material becomes deprived of the power of producing anthrax infection. The same obtains with other highly specialised, bacteria, e.g. the streptococci, the typhoid fever bacillus, and others. While this process of killing off of the more specialised and less assimilative bacteria by the more rapidly growing and more assimilative bacteria is essentially a survival of the fittest in the struggle for existence, there is another factor to be considered that not immaterially helps to bring about that result: it is the inimical influence the chemical products of the saprophytic bacteria have on the more sensitive and more highly specialised pathogenic bacteria. If, for instance, a filtered solution is made of a putrid albuminous substance, the putrefactive bacteria being all removed, and of this solution a considerable amount is added to an otherwise favourable nutritive material, e.g. alkaline broth, it will be found that this mixture is unfavourable for the growth of some species, in some cases more than in others. To the same class of inimical influences belongs the influence of fæcal matter on various species of bacteria, e.g. anthrax bacilli, cholera spirilla, and the typhoid fever bacillus investigated by Kitisato. His results on the death of cholera spirilla in fæcal matter are instructive. They are published in the 'Zeitschrift f. Hygiene,' V. p. 487.

Of a similar character are the observations recorded by Garré ('Correspond. f. schweizer. Aerzte,' XVII. 1887), who showed that nutritive gelatine which has already served for the growth of bacillus fluorescens putidus—a common saprophyte in water and putrid fluids—is no longer capable of serving the growth of some bacteria: e.g. the bacillus of Friedländer, typhoid bacillus, pink torula, staphylococcus pyogenes aureus; while others are capable of growing in such gelatine, though slightly retarded: e.g. cholera spirillum; and still others grew normally: e.g. Finkler's spirilla, bacillus anthracis. Towards the former, therefore, the bacillus putidus has a decided *antagonistic* action, while with the latter it is symbiotic. But this antagonism, when existing, is not necessarily mutual, for while the typhoid bacillus renders the gelatine also unfit for the growth of the bacillus fluorescens putidus—these two species being mutually antagonistic—it is not so with the bacillus of Friedländer or the staphylococcus aureus. Diphtheria bacilli can grow well in broth previously exhausted by proteus vulgaris.

To the same category belong the observations of Soyka and Bandler, who studied the manner in which certain bacteria are capable of growing in media previously exhausted by other bacteria ('Fortschritte der Med.' 1888, p. 76).

Cash has made similar observations with bacillus anthracis and certain micrococci when growing simultaneously. He found that the growth of the bacillus anthracis does go on to a certain extent, but that the virulence of it is impaired by the growth of the micrococci. This subject deserves a more exhaustive study than it has hitherto received. It is mainly of importance to ascertain whether and to what extent an inimical influence is exerted by one species on the other capable of growing simultaneously in the same medium. There is good reason for supposing that hereby, in some cases at any rate, one species is capable of attenuating the virulence of another. Thus in the cultures which Pasteur used as attenuated cultures for producing protective inoculation in fowl cholera, it was not, as Pasteur believed, the prolonged exposure to air that produced the attenuation of his cultures, but the impurity of his cultures (Kitt), and likewise the attenuated condition of the culture fluids that Pasteur used for protective inoculations against swine erysipelas, were probably caused by the impurity of the culture fluid (Schütz); there being present in Pasteur's fluid, besides the true bacillus of swine erysipelas, a contaminating micrococcus.

Watson Cheyne, Von Emmerich ('Archiv f. Hygiene,' VI. 1887), and others showed that the streptococcus erysipelatos possesses a similar attenuating influence on the bacillus anthracis, for by inoculating simultaneously pure cultures of the two microbes into rabbits they were able to show that the bacillus anthracis was unable to produce fatal anthrax, though when separately inoculated it exerted its full virulence. It depends, however, to a considerable degree how much of the one and how much of the other microbe is injected in order to produce this inhibitory effect, for if too little of the streptococcus be injected the bacillus anthracis will exert its full virulence, or *vice versâ*. This whole subject is obviously a very important one from a practical point of view—from the point of view of finding antidotes against the action of pathogenic bacteria—and it deserves greater attention than it has hitherto received.

The writer has himself made some experiments with regard to injecting simultaneously two species. In one series the bacillus of fowl enteritis was grown in broth with the swine fever bacillus; in the other, the bacillus of swine erysipelas with that of swine fever, but neither in the amount of multiplication nor in the virulence of the swine fever bacillus could any change be noticed. He has, however, succeeded in neutralising the fatal effect on mice of the grouse bacillus, if at the same time the aërobic malignant œdema bacillus (*see* later) be injected.

Bouchard, Charrin, Woodhead and C. Wood have shown that there exists a strong antagonism between the bacillus pyocyaneus or its products and the bacillus anthracis; so much so that upon the injection of the former, simultaneously with or immediately after the latter, into an animal susceptible to anthrax, this latter disease does not take place at all, whereas a control animal not treated with the pyocyaneus succumbs to anthrax.

It is well known that certain infectious diseases, of which infection occurred simultaneously in the same body, do not take place simultaneously, but that the one probably has to wait, as it were, till the other has gone through its course. In other cases one disease has clearly an inimical influence on another. Take, for instance, the observations repeatedly made by surgeons that erysipelas has a curative influence on certain tumours; Fehleisen had by direct experiment with pure cultures of streptococcus erysipelatos proved that certain sarcomata can be made to disappear and a cure effected by producing erysipelas in the skin of the part.

But there is a converse side to this, namely the question whether, and if so, to what extent, one condition, one species of bacteria or its products, enhances the power of multiplication and the action of another. Monti ('Ac. d. Linc.,' October 6, 1889) pointed out that the culture of the diplococcus pneumoniæ—which, as is well known, gradually (by age and by continued subcultures) loses its virulent action on animals—regains the virulence if injected simultaneously with broth culture of the common saprophyte proteus vulgaris, from which the bacilli themselves are previously removed or killed by heat. This increased virulence of the pneumococcus may be achieved either by injecting this and the proteus culture at the same place, or at distant places simultaneously or soon after one another. The writer has similarly found that cultures of streptococcus of erysipelas, which had lost their action on rabbits, regained virulence if injected mixed, i.e. simultaneously, with broth culture (four days old) of the proteus vulgaris; and it made no difference whether the latter culture was or was not previously sterilised.

Charrin and Roger ('La Semaine Méd.,' 1890, No. 4) show that while normal rats are, as is known, very little susceptible to anthrax, they become highly susceptible if by working at a treadmill they are made fatigued, and H. Leo ('Zeitschrift f. Hygiene,' VII. 3) finds that by the presence of much sugar in the blood and tissues the susceptibility to anthrax and tubercle is not increased, while for glanders it becomes greatly enhanced. Phloridzin is administered in small doses with the food, sugar thereby becoming present in the tissues. Rats thus prepared resist anthrax as much as unprepared rats, guinea-pigs first prepared with phloridzin and then inoculated with tubercle do not show more intensive or more rapid tuberculosis. While normal white mice are almost insusceptible to glanders, they become highly susceptible to such infection, if prepared with phloridzin. Mya and Sanarelli give an account ('Fortschr. d. Med.,' IX. No. 22) of a large number of experiments, in which by introducing acetylphenylhydrazin into an animal insusceptible to a particular disease this animal becomes thereby susceptible. This substance is known to produce destruction of the red blood corpuscles (Gottstein) and hæmoglobinæmia; pigeons and rats thus prepared proved susceptible to anthrax.

CHAPTER VIII

BACTERIOSCOPIC METHOD OF EXAMINING WATER, AIR, DUST, FOOD

An important branch of bacteriological research of water, air, &c., has been opened by Koch's gelatine method of plate cultivation as illustrated by the researches of Koch, Angus Smith, Hesse, Wolffhügel, Heyroth, Hochstetter, P. Frankland, Carnelly, Fraenkel, Kraus, Karlinsky, and others in accurately determining the number and, what is of far greater importance, the nature of the microbes present in water, soil, air, sewage, and various other materials, such as milk and a variety of other foodstuffs.

In all these researches a definite quantity (measured or weighed as the case may require) is added under proper precautions to nutrient gelatine (about 5 or 6 c.c. in a test tube); this is then liquefied in warm water, well shaken up and poured on to a plate. The character of the colonies and their number is then studied and easily ascertained, subcultures of the isolated colonies are made, and these further investigated. If the number of microbes suspected to be present in the materials be great, of course only small quantities must be used for the plate cultivations, or better still a small quantity should be previously diluted with a large quantity of sterile water or salt solution, and then of this a measured small quantity is used for each gelatine plate. The counting of the colonies in the plate cultivation is carried out by means of ruled plates. The writer uses for plate cultivations circular shallow glass capsules of the same diameter; this diameter being known permits of ascertaining the area of the plate either in square inches or centimetres. For counting the colonies, if the number of them be too large, and in order not to altogether lose the experiment, the plate is placed on a slate ruled in square half-inches or centimetres, and then the colonies, ten or twelve, are counted in squares, the average is taken and multiplied by the area of the plate. An example will illustrate this: the number of colonies in the plate being too great to be directly counted, the plate dish is placed on a slate ruled in square half inches; the average number of colonies in one square half inch (as a result of counting them in ten squares) is twenty-two, the plate dishes have each an area of thirty-two square half inches, therefore the number of colonies present in the above plate is approximately 704. Now, for one of those plates in the experiment in question 0·5 c.c. of tap-water was used, consequently this particular tap-water contains 1,408 microbes per c.c.

Another mode of determining with exactness the number of colonies present, if moderately great, in a plate dish, is to invert the plate dish and then with a pen to draw lines on the glass dish so as to subdivide the area into four, eight, sixteen, or thirty-two as the case may require, and then to count seriatim the colonies in these areas. If the number of colonies present in a plate be limited, say 20 to 50, of course there is no difficulty in directly counting them.

It is advisable to at once prepare more than one plate, in order to obtain a more accurate result as to the number of colonies.

1. *Water.*—By means of a sterilised graduated pipette a small quantity —0·1 to 0·5 c.c.—of the water is added to a gelatine or agar tube for each plate dish. If the water is notoriously very rich in microbes, the quantity added must be of course much smaller, only $\frac{1}{100}$ to $\frac{1}{50}$ c.c. The writer uses for this and other similar determinations a set of graduated capillary pipettes of exactly the same kind as are used in the Hæmocytometer,[1] 10 c.mm. 20, 50, 100, 250, 500 c.mm, and 1 c.c. A short india-rubber tube, with a mouthpiece into which a small plug of sterile cotton-wool is pushed, can be easily fixed at the upper end of the pipette and this is then ready for use. The pipette before being actually used for measuring is filled by drawing up into it solution of bichloride of mercury (1 in 1,000) once or twice, then washed out well in the same way with sterile (boiled) distilled water, and next with the fluid to be tested. A measured quantity of the fluid is then drawn up (10 c.mm., 20, 50, 100 c.mm. or 1 c.c. as the case may require) and blown out into a gelatine or agar tube; this is then used in the ordinary way for a plate dish.

In the case of the ordinary London drinking water—tap-water—0·5 or even 0·25 c.c. yields sometimes too many colonies to be easily counted. When making a first examination of water of unknown character it is advisable to make several plate cultivations, one with 20 c.mm., one with 100 c.mm., and one with 250 c.mm.; thereby the amount is determined necessary to use for a plate for convenient counting.

In the case of ordinary London sewage even 10 c.mm. yield far too many colonies to be counted easily; add therefore 0·5 c.c. of the sewage to 99 c.c. of sterile water, and of this take 5 c.mm. for one plate.

The number of the bacteria present in London drinking water of various sources and under various conditions has been investigated by Dr. Percy Frankland; especially their morphological, biological, and chemical characters have been the subject of special study by this observer, and we must refer the reader to his papers in the 'Proceedings of the Royal Society,' and in the 'Phil. Transactions,' where they are fully described. As to the difference of water when fresh and stored, see Bischoff, Percy Frankland, and others.

2. *Soil.*— The method which the writer uses to isolate, to count, and to determine the character of the bacteria present in soil, dust, &c., is this: One gramme of the material is added to 1,000 c.c. of (boiled) sterile distilled water, while still warm; it is then shaken up repeatedly for from fifteen to twenty minutes; the mineral matter is allowed to subside and plate cultivations are made of the fluid as above. Ten c.mm., 20 c.mm., 100 c.mm. are added each to one gelatine or agar tube, to be used for one plate each.

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[1] Mr. T. Hawksley, of Oxford Street, made for us a very useful case containing these graduated capillary pipettes, with india-rubber tubes and mouthpiece.

The number and character of the organisms in soil and dust (taken from the plugging or deafening material of the floors of dwelling-rooms, &c.) has been investigated by Emmerich, Percy Frankland, Carnelly and Miss Johnston and others. The character of the microbes has been studied by Dr. and Mrs. P. Frankland (On Nitrifying Organisms, *see* a later page). Hæreus describes four different species in the soil, of which he maintains that they are nitrifying microbes.

3. *Air.*—Miquel, Hesse, P. Frankland, Carnelly, Robertson and others have investigated the number of microbes present in various samples of air, under various conditions (town air, country air, mountain air, air of schools, dwelling-rooms, hospitals, &c.). The method is always in principle this: by means of an ordinary gas clock or gasometer a measured quantity of air is drawn at moderate rate by means of an aspirator—fall of water or mercury—through a cylindrical tube (Hesse), or through a flask (Frankland, Carnelly) containing a thin layer of solidified nutrient gelatine. Hesse's tubes are cylindrical, in which nutrient gelatine while still liquid has, by slightly rolling the tubes, set at one side in a thin film; they are plugged at each end with a sterile india-rubber stopper containing a sterile glass tube; to each is fixed a sterile tube, one is connected during the experiment with the gas clock, the other with the aspirator; the time during, or the rapidity with which the air is drawn through and the amount of air so drawn through are accurately noticed; after the experiment the glass tubes are plugged with cotton wool so as to serve as a filter against the entrance of further microbes. In Dr. P. Frankland's experiments, the air is passed through a sterile plug (asbestos or glass wool) contained in a tube or flask, and this having retained all microbes is then thrown into the gelatine; this is liquefied and well shaken so as to wash out of the plug all microbes and to uniformly distribute them in the gelatine. The gelatine is then used for making plate cultivations in the ordinary plates, or is set as a thin film on the inside of the flask. The writer uses a glass tube four to six inches long, half an inch wide, containing in the middle a cotton wool or glass wool plug about one and a half to two inches long; at each end the tube is plugged with a small cotton-wool plug. One end is drawn out in the shape of a large canula; the whole is sterilised. When used the plugs of the ends are removed, the canula end is joined to an aspirator and air is drawn through; at the end of the experiment the ends are again plugged. In order to use it afterwards for plate cultivations, the plugs of the ends are removed, the central plug is then pushed out by means of a thin glass rod, placed in liquefied nutrient gelatine or agar, well shaken, and then plate cultivations are made.

In Carnelly's experiments the nutrient gelatine is allowed to set at the bottom of a large sterile flask, the mouth of which is closed by a sterile india-rubber stopper, through which two glass tubes are passed—one long one through which the air passes from the gas meter, the other a short one connected with the aspirator: as the air passes into and out of the flask the microbes are deposited on the surface of the set gelatine.

4. Milk is treated in the same way as water; so also various table waters, seltzer water, soda water, &c.

5. Fæces and various substances more or less solid are treated in the same way as was mentioned of dust and soil.

6. Ice of different sources has been examined; a lump of ice is washed on the surface with sterile water, then from the middle a piece is chipped out and placed in a sterile test tube; immediately upon being melted a definite quantity of the ice water is taken for plate cultivations in the same way as for water analysis.

As regards the character of the microbes present in ordinary cow's milk in ice, in fæces, see the papers by Escherisch, Hueppe ('Mitth. aus d. k. Gesundh.' II. 1884), Heim ('Mitth. aus d. k. Gesundh.,' V.), Brieger, Bienstock, and Escherisch, Heyroth,[1] Hochstetter,[2] C. Fraenkel, and others.

It ought to be mentioned, however, that to obtain an accurate knowledge of the exact number of microbes present in any material, it is not sufficient to examine the material by gelatine plate cultivations alone: errors of a considerable degree have been made in this respect, inasmuch as the number of microbes ascertained by the gelatine plate method has been shown to be lower—in some cases considerably so—than the actual number present in the materials, as ascertained by other methods. For this reason it is necessary to supplement the gelatine plate cultivations by agar plate cultivations. Fol has shown to what enormous errors one may sometimes be led by estimating the number of bacteria in water by the gelatine method alone; it has been repeatedly mentioned in previous chapters that there exist numerous species, some very important, which do not grow at 20° to 22° C., i.e. at temperatures at which gelatine plate cultivations are kept.

CHAPTER IX

ACTION OF BACTERIA

Chemical Function

It would carry us beyond the scope of the present article were we to attempt to describe in detail the results of the numerous researches carried out by a host of investigators in connection with the specific chemical activities of bacteria and fungi. This subject has made important and remarkable progress within the last ten years, but it may be said to have in reality only recently seriously commenced. The researches of Pasteur, Cohn, Nencki, Fitz, Prazmowski, Brieger, Hueppe, Winogradski, and in this country P. Frankland, Warington and others, have brought to light a vast number of important facts; to the pathologist and sanitarian those of Selmi, Brieger, Bouchard, Hankin, Sidney Martin, Allan Macfadyen, Fraenkel, Behring and others, dealing with the chemical products of bacteria, so far as they are capable of affecting the animal system, must as a matter of course have precedence over those which, though interesting, are so more or less only from a general biological point of view.

It has now been shown that by bacterial life, outside or inside the body, alkaloidal substances are produced which belong to two kinds: some belong, judging from particular chemical reaction, to the group of alkaloids first demonstrated by Selmi, and called by and after him *ptomaines*; these substances are, if one might say so, the result of general activity of a large group of bacteria capable of producing putrefactive decomposition of proteids. Another kind are due to some more specialised microbes, and are of a specifically poisonous nature; they are said to be different in composition from the former and are called *toxines*; such are the poisonous substances demonstrated by Brieger, Wooldridge, Roux, Hankin, Martin and others from pathogenic microbes growing in artificial media; and it is believed that the same poisonous principles are also produced by them within the animal body (anthrax, diphtheria bacillus, and tetanus bacillus); and it is by such substances that within the affected body the particular infectious malady is produced. To this group belong the toxines formed by the bacillus anthracis isolated by Hankin, Sidney Martin, Fraenkel, and others.

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[1] *Arbeit. aus d. k. Gesundh.* IV. p. 1.

[2] *Arbeit aus d. k. Gesundh.* II. p. 1.

The exact chemical nature of these toxines is not determined, for some maintain that they are albumoses, others consider them as alkaloids, and others again compare them to ferments.

Reviewing the chemical function of bacteria, it will be found to be a manifold one:—

(1) In the first place some have a specific fermentative action. The proteolytic or peptonising action is a widespread one, both amongst putrefactive and non-putrefactive bacteria; albuminous substances so essential to the life of many species of bacteria by it are rendered soluble and available for these. Claudio Fermi published in 'Archiv f. Hygiene,' X. No. 1 an extensive research on enzymes produced by various septic and pathogenic bacteria, their nature and dependence on the nutritive media, and their non-identity with the various toxines. The production of acetic acid and lactic acid is also common to many organisms; then the action in converting urea into carbonate of ammonium, the mannite fermentation, the dextrose and indigo formation belong to this category, viz. specific fermentative action; so also the butylic alcohol fermentation of fatty and starchy matters, and the ginger-beer fermentation (Marshall Ward, 'Proc. of the Royal Society,' December 12, 1891). (On lactic acid fermentation *see* Pasteur, Lister, Hueppe, Grotenfelt, and Marpmann.)

(2) The nitrifying power is, according to Haereus ('Zeitschrift f. Hygiene,' 1886), common to many soil bacteria. The first of these actions is of necessity one that has a general, and one may say a very high importance, inasmuch as it is the great process by which certain nitrogenous bodies, like the salts of ammonia, are converted into nitrites and nitrates so essential to the vegetable kingdom; but neither the assertion of Haereus nor of Schloesing and Müntz, who claim to have isolated 'nitrifying microbes,' can be accepted, for Winogradski,[1] G. Frankland, and Warington [2] have shown that the microbe which converts ammonia salts into nitrites is different from that which converts nitrites into nitrates.

(3) The pigment action. The actual position and value of this is not yet well understood. The power to form pigment, generally dependent, *cæteris paribus*, on free oxygen (except in a few cases: spirillum rubrum), is very general, and, one would suppose, must be playing some great *rôle* in nature. Erdmann first pointed out the similarity existing between certain aniline dyes and the pigment produced by bacillus prodigiosus; Schrötter has minutely investigated this, and found that its pigment bears in every respect a striking resemblance to fuchsin.

(4) The production of substances acting as poisons on the animal body. This must be taken to be as much a specific action as that of pigment. As has been mentioned above, while some of these poisonous substances correspond to the group of alkaloids known as ptomaines, others are of the nature of albumoses (Hankin, Martin, Fraenkel, and Brieger). It is known through Selmi, Brieger and others that in some of the common putrefactive processes of albumen, poisonous alkaloids, the ptomaines, are produced; but it must not be supposed that only in putrefactive processes are these poisonous alkaloids generated, nor that all alkaloids produced in putrefaction are poisonous (Brieger).

(5) The pathogenic action, in other words, the power to produce in the animal body definite pathological changes, that is, a definite infectious disease.

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[1] *Annales de l'Institut Pasteur*, iv. 4 and 5, v. 9.

[2] *Chemical News and Proceed. of the Royal Society*, 1891.

But on more carefully looking at such action in the light of the researches published during the last few years it appears that this pathogenic action depends entirely on the power of certain bacteria to produce toxines, and poisonous albumoses; and further it has been shown that such poisonous substances are actually isolable from the tissues of the diseased animal body. These poisonous substances are also elaborated by the bacteria outside the body (i.e. in artificial cultures), and when they are introduced separately, but in sufficient quantities, into an animal, the same pathological changes are thereby generated as when the bacteria work within the body; it has also been shown that by graduating this quantity of the poisonous substances, a mild and transitory illness may be induced, which in some instances is for some time protective against a second attack.

(6) As an action not generally considered a specific fermentative one is the putrid decomposition of albumen by certain bacteria, e.g. proteus vulgaris, bacillus fœtidus, and others, which, growing and multiplying in proteid materials, break these down into lower nitrogenous principles (leucin, tyrosin, indol, skatol, and phenol), while at the same time foul gases like NH_3, H_2S, H, CO_2, and CH_4 are evolved; but it is a question whether this putrefaction is not as much a specific fermentative action, as for instance the peptonising action of bacteria or the acetic, lactic, and butyric fermentation; and further, it is not decided whether in all decomposition of albumen during putrefaction this is always brought about by the action of a single species, or whether in some instances of putrefaction several species are at work in the different phases of the process.

PATHOGENIC ACTION

In a former chapter we have shown that many bacteria cannot multiply within the normal tissues of the animal body; such bacteria, termed saprophytes or septic bacteria, do not produce pathogenic results when introduced into the normal tissues. But here again we have to differentiate those that, though saprophytes, can nevertheless assume the character of parasites when the normal character of the tissues is lost, as will be shown later on in various examples. From these septic bacteria must be distinguished those that can live and multiply within the normal living tissues. But in this last respect there exist the greatest differences: (*a*) while some species, as we have mentioned on a former page, are capable of doing so in one species of animals, they cannot do so in another; (*b*) some species, although their natural breeding ground is the normal body of an animal (secretions, mucus, &c.), in which, however, they produce no pathogenic effect, when introduced into the tissues of another animal show definite pathogenic action; (*c*) again some species producing in one set of animals (and man) a constant well-defined pathogenic action of one kind, when transferred to a different kind of animal produce a different though constant pathogenic action; further: (*d*) some species producing a definite pathogenic action in the animal body are capable of retaining this power unimpaired when growing outside the animal body, while other species manifest definite pathogenic action only when they have grown in the animal body and have been transferred from this directly to another animal body; when growing outside the animal body, in artificial media, they gradually lose this pathogenic power, some rapidly, others slowly; some of them, when growing under certain conditions (altered nutritive material, a different animal body), can again assume their pathogenic action, while others have apparently lost it permanently.

We proceed to illustrate these different groups:

(*a*) Bacteria capable of multiplication and of producing disease in one but not in another animal. Most bacteria known to possess decided pathogenic power come under this category. The bacillus anthracis, while pathogenic for man, rodents, and herbivorous animals, has not this power, or only slightly so, on carnivorous animals, or on rats; bacillus mallei, bacillus tuberculosis, bacillus lepræ, bacillus choleræ gallinarum, spirillum of relapsing fever, (micrococcus) staphylococcus pyogenes, streptococcus erysipelas, streptococcus scarlatinæ, bacillus of fowl enteritis, bacillus of swine erysipelas and swine fever, bacillus of typhoid fever, diplococcus pneumoniæ, and a host of others, belong to the group of bacteria which, though specific to one animal, are without pathogenic action on another. When they cannot produce a pathogenic effect, the animal is spoken of as insusceptible, and we have explained this condition by ascribing to the blood and lymph in this animal the power to kill the particular bacteria, or at any rate to inhibit their multiplication.

(*b*) There are several species of bacteria known, which, although derived from non-pathological materials, nevertheless possess the power of effecting definite pathogenic results in some animals. The capsulated bacillus known to occur in the normal fluid of the mouth (human), produces in the rabbit, when subcutaneously inoculated, a well-defined septicæmia (Pasteur, Sternberg). In human sputum (normal or pathological) there occur various species of bacteria, some of which (streptococcus, bacillus of Friedländer, diplococcus pneumoniæ) have the power to produce septicæmia in rodents. In normal human fæcal matter Brieger isolated a short bacillus which produces septicæmia in the guineapig; likewise Bienstock isolated a thin bacillus which is capable of causing septicæmia in mice. Von Emmerich's bacillus isolated from choleraic evacuations—the Naples bacillus—probably the same as Brieger's bacillus—causes likewise septicæmic infection in guineapigs. Koch's and Finkler's spirilla both act under certain conditions of experimentation like pathogenic microbes on guineapigs. Koch's septicæmia in rabbits, Davaine's septicæmia in rabbits, Koch's septicæmia in mice are caused severally by microbes occurring in putrid animal materials. The typhoid bacillus of Eberth, Koch, and Gaffky is capable of causing septicæmic infection in mice. The micrococcus tetragonus occurring in the purulent matter of tuberculous deposits (lung, and other localities) has a powerful septicæmic action on guineapigs (Gaffky).

(*c*) In this group may be mentioned the typhoid bacillus just referred to; which, however, it must be added, has not been as yet satisfactorily proved to be really the cause of typhoid fever: the evidence on this point is, though strong, not complete. This microbe, when introduced in more than minimal doses, produces septicæmic infection in mice; but this result is acute, the animals die in from one to three days with the symptoms of septicæmia, and the bacilli are present in the blood of the general circulation. The diplococcus pneumoniæ of Fränkel and Weichselbaum, when from recent sub-cultures, causes general septicæmic infection in guineapigs and mice.

The spirillum of Koch and that of Finkler, when inoculated in considerable doses subcutaneously in mice and guineapigs, both sometimes cause septicæmic infection with the comma-bacilli in the blood of the general circulation. The staphylococcus aureus liquescens causes abscess, in some instances, when inoculated into rabbits, but in many other instances when injected into the vessels of rabbits and guineapigs produces a general septicæmic infection. So also the streptococcus pyogenes derived from human abscess occasionally causes general septicæmic infection in rabbits and guineapigs.

(*d*) Many bacteria of well-ascertained pathogenic power lose this gradually, owing to successive cultivation on artificial media, or to varied conditions of cultivation. Examples illustrating these points are very numerous. The bacillus anthracis, so long as it is cultivated at ordinary temperature, or at a temperature up to 38° C. in neutral or very faintly alkaline broth, in neutral or faintly alkaline nutrient gelatine, on nutrient agar, or boiled potato, retains full virulence; Buchner is incorrect in asserting that by successive cultivations in broth the bacillus anthracis gradually loses all virulence. But there are numerous pathogenic bacteria which by gradual cultural removal from their original breeding-ground, i.e. the animal body, lose all pathogenic power; e.g. the bacillus of diphtheria, the diplococcus pneumoniæ, the bacillus of Middlesbrough pneumonia, the streptococcus erysipelatos, the streptococcus scarlatinæ. And various species of bacilli causing septicæmia in rodents are of this category, e.g. the bacillus of Davaine's septicæmia, of Koch's septicæmia in rabbits, of malignant œdema, and others. While at first, i.e. directly derived from the human or animal body, they act virulently, and also possess this character in the first few sub-cultures, they lose this power—some sooner, some later—on continued cultivation. The spirillum of Koch is of the same nature; the sub-cultures of this microbe carried on for a large number of generations become certainly attenuated in so far as their action on the guineapig is concerned. Others, like the bacillus anthracis, bacillus choleræ gallinarum, bacillus of fowl enteritis, bacillus tuberculosis, bacillus mallei, bacillus of swine fever and of swine erysipelas, do not show any attenuation when the cultivations are carried on under unaltered conditions of temperature and soil. But if either the nature of the medium, or the temperature in which the sub-cultures are kept, becomes altered, these also undergo gradual attenuation, and may even lose the power to produce any pathogenic effect. The bacillus anthracis grown in broth at 42–43° C. undergoes distinct loss of virulence after eight to twelve days, and after fourteen to sixteen days altogether loses the power of producing fatal infection; when grown under unsuitable conditions of soil it also undergoes attenuation which may lead to the complete loss of pathogenic effect (Buchner). When the bacillus anthracis is grown in the mouse its virulence becomes attenuated, inasmuch as it does not produce fatal anthrax in sheep; when derived from the sheep or cattle its virulence is greater than when grown in the mouse or guineapig; when the bacillus anthracis is grown for a week or two on alkaline nutrient agar its virulence is less than when grown in slightly alkaline broth. The bacillus of swine erysipelas when passed through a succession of rabbits is attenuated as compared with the bacillus derived from the pig. The bacillus anthracis, the bacillus of fowl cholera, the bacillus of swine erysipelas when grown as impure cultures lose their virulence. The bacillus tuberculosis when grown at temperatures between 35–37° is less virulent than when grown at 38–39° C.; when grown on Koch's solid serum at 37–39° C. it retains its full virulence through numerous sub-cultures, while when grown on nutrient glycerine agar (Roux and Nocard) through a few sub-cultures it loses a great deal of its virulence.

The bacillus tuberculosis derived from bovine tubercles is more virulent for the guineapig and rabbit than that derived from the human tubercle; and the former produces general tuberculosis in guineapigs and rabbits in a considerably shorter time and more extensively than the latter. But it must be added to all these considerations that by growing these microbes again on the most favourable soil and under the most favourable condition of temperature the full pathogenic action is, as a rule, again attained, if not in the first at any rate in the subsequent sub-cultures. When the bacillus anthracis is grown for a fortnight in faintly alkaline chicken broth at 42·5° C., it will be found to have lost its virulence altogether, but on inoculating fresh chicken broth from such a culture and keeping it at 35–37° C. for a few days, a culture is produced which possesses renewed virulence, and after another sub-culture its full virulence is recovered. On growing bacillus anthracis in nutrient gelatine to which perchloride of mercury is added in the proportion of 1 perchloride of mercury to 40,000 nutrient gelatine, the resulting growth fails in many instances to produce fatal anthrax ; so does the sub-culture in a new set of medicated gelatine ; but if from such an attenuated culture a fresh sub-culture is made in normal nutrient gelatine, virulent bacilli are again obtained. The same holds good for other microbes which have become attenuated by one cause or another. Take, for instance, the case of attenuation produced by growing in subsequent cultures the bacillus pneumoniæ (Middlesbrough) ; while at first the cultures of this bacillus are very virulent for mice, this effect is gradually lost as the sub-cultures are carried on through several generations, but when of such attenuated bacilli cultures are made in alkali-albumen the virulence of the bacilli is again recovered. Hueppe shows that by growing the spirillum choleræ and spirillum of Finkler in egg, closed after inoculation so as to ensure an anaërobic condition, a very poisonous culture is produced. Van Ermengen has shown that by growing the spirillum choleræ in aqueous humour a much more poisonous product is obtained than by growing it in broth. The streptococcus scarlatinæ by successive cultivation in broth gradually loses its virulence on mice, but by again growing it in alkali-albumen a virulent growth is recovered.

In all these cases of attenuation, through one cause or another, the morphological and biological characters of the microbes remain practically unaltered ; in all cases their microscopic character, the manner of their growth in plate, streak, and stab cultures remain very nearly the same, and from the study of these alone no alteration of their function could be recognised. It is important to bear this in mind, viz. that, so far as actual and careful observation hitherto shows, there is no definite morphological alteration going on hand in hand with the alteration in virulence ; Buchner maintained that as bacillus anthracis in his sub-cultures gradually loses its virulence, it morphologically gradually becomes more like the motile hay bacillus, and he at first went so far as to say that not only does the anthrax bacillus in this course of attenuation and complete loss of its pathogenic power become the motile hay bacillus or something similar to it, but the typical motile hay bacillus can by cultivation become the non-motile virulent anthrax bacillus. All these and similar assertions must be held to be disproved by numerous observations carried on by exact methods of cultivation. The motile hay bacillus can no more assume the pathogenic character of the anthrax bacillus than a common non-poisonous snake can become an adder, though an adder by drawing its poison-fangs and poison-bags can become a non-poisonous snake ; the offspring of such an artificially made non-poisonous adder are none the less poisonous adders.

It will be readily understood from the above considerations that cases may occur when one organism bears a striking morphological and biological resemblance to a pathogenic one, or to one of a similar though weakened pathogenic action ; in such cases it is quite possible that they may have a genetic relation to one another, that is to say, the pathogenic species may have through one cause or another lost its pathogenic power, or this particular action may have become modified, but still the microbe may have retained all its morphological and biological characters. We will illustrate this by examples. The streptococci are a very numerous family, many species of streptococci resemble one another in their morphological and biological characters ; the streptococcus erysipelatos, the streptococcus pyogenes, the streptococcus scarlatinæ are by some observers considered to be genetically related to one another, inasmuch as they maintain that the streptococcus erysipelatos may become modified into the streptococcus pyogenes and that this is only the same as the streptococcus scarlatinæ. The action of the streptococcus pyogenes is uncertain, as in some cases it causes abscess, in others it does not; the streptococcus scarlatinæ causes in some cases no other action than the streptococcus pyogenes, and finally the streptococcus erysipelatos in some cases does not produce any other action than that of the streptococcus pyogenes. Now, from an extensive and long-continued study the writer has come to the conclusion that these assertions are not in harmony with the facts, because the real streptococcus erysipelatos is in functional respects totally distinct from the others; what is described as streptococcus pyogenes comprises a number of different species, and the streptococcus scarlatinæ can be morphologically, biologically, and functionally distinguished from the streptococcus pyogenes. We may add to these species also two other streptococci: the streptococcus of the Edinburgh cow disease and the streptococcus of human puerperal septicæmia. We cannot therefore agree with those observers who do not distinguish between these different species, although we agree with the general proposition that each one of them by successive cultivation on gelatine after some time does gradually lose its original pathogenic function.

Hueppe described a non-motile bacillus which he cultivated from soil, and which he finds in morphological and cultural characters very difficult to distinguish from bacillus anthracis, yet according to him it does bear a certain relation to this latter, inasmuch as it—the former—inoculated into mice, gives protection against the latter, although itself it does not cause anthrax. Hueppe is inclined to think that this species of bacillus may have once been bacillus anthracis, but have lost its pathogenic power. Now, assuming that Hueppe's observations as to the protective power of that soil-bacillus against the bacillus anthracis be a reality, we still find that this latter, on its change into the former, has retained its morphological and biological characters.

The important question that presents itself is—What causes in some bacteria this attenuation in function?

On a former page we have mentioned that in several instances it has been shown that the chemical products of certain pathogenic bacteria, when injected in certain quantities, have the power of causing a mild form of the particular disorder, and thus to protect against the virulent disease; and we have also mentioned that these protective chemical products are elaborated by the bacteria, not in all, but only in certain media. Thus it is known that the anthrax bacilli grown in broth do not form those toxic substances in any appreciable quantity: Wooldridge's success was only achieved by growing the bacilli anthracis in certain albuminous fluids. Then we mentioned that Van Ermengen has shown that the chemical products of the choleraic spirilla in aqueous humour, and in the intestinal fluid of the intestine of guineapigs, and Hueppe that those grown in eggs are infinitely more poisonous than when grown in broth. We have also seen that certain other bacilli and micrococci when grown in alkali-albumen regain poisonous action, when by previous successive cultivation in gelatine they had lost it. From these facts, it seems that the conclusion is justified that the virulent activity of pathogenic bacteria (that is the production of the toxines) depends, *cæteris paribus*, in a great measure on the medium or the soil in which they, the bacteria, grow. We might suppose that owing to certain substances being absent from, or other substances being added to, the original soil in which the bacteria multiply, or that owing to certain other conditions, such as temperature, obtaining in their growth, the chemical activity of the bacteria becomes changed, and that the result of their own chemical constitution and of the molecular changes brought about by those so altered bacteria also becomes changed. And we would further conclude from these facts that a bacterium itself chemically changed, and altered in its chemical action, would manifest a different chemical action at least for one generation when again transferred to the suitable soil. There can be little doubt, and it is now generally agreed, that in the pathogenic action of bacteria it is not merely their presence in numbers nor their mechanical effects which cause the disease, but that it is by their chemical products, by their toxines, that they manifest their poisonous action, that it is the character and amount of these chemical substances which determine the peculiar pathological states characterising the different diseases caused by the bacteria. In anthrax, though the number of bacilli in the blood and spleen is, as a rule, great just before death, it nevertheless can only be owing to their particular specific chemical action that the disease is brought about; in many specific diseases the number of the bacteria is not large enough to cause mechanically those grave local and general effects that we meet with; besides, the character of the changes is so utterly different in the different diseases. This undoubtedly must be due to specific chemical action, i.e. to action of the toxines of those bacteria, differing in nature and in amount in the different cases. This is confirmed by the observations above stated, according to which it has been possible to obtain these poisonous substances in artificial cultures and to separate them from the bacteria themselves. Add to this also that a powerful necrotic influence is exerted by some bacteria over considerable areas of the tissue in which they grow, e.g. in swine fever, certain septicæmia bacilli, the tubercle bacilli, and the diphtheria bacilli.

We can readily understand that if the bacteria, owing to one cause or another, have undergone a modification in their chemical constitution and chemical activity, their poisonous products which cause the virulent disease may have become modified either in character or in amount or both, and that such modified bacteria will not be able to produce the same results, either as regards intensity or the character of the disease, as the unmodified bacteria. Under the same theory we can also understand how certain bacteria growing in the blood produce a different effect from that which results from the same bacteria growing in the subcutaneous tissue, e.g. the bacillus of swine erysipelas, or the bacillus of symptomatic anthrax. In the former case the bacilli after injection into the blood-stream produce a mild disorder, but growing in the subcutaneous tissue produce a severe fatal disease. In the first case the chemical conditions evidently cannot be the same as in the latter; while for other microbes just the reverse is the case, viz. when growing in the subcutaneous tissue the disease produced is milder than when they are growing in the blood, e.g. in small-pox; inoculated small-pox is milder than small-pox in which the contagium has passed (by the respiratory organs) into the circulation.

In connection with the chemical products of specific bacteria there is one question which it is important to clearly understand and to define, viz. the question of the exact nature and meaning of infection. In the first place it is necessary to remember that it has been proved for several pathogenic (in the wider sense) species of bacteria—bacillus anthracis, spirillum choleræ Koch, spirillum Finkler, several species of septicæmic bacilli, bacillus diphtheriæ—that also outside the animal body they can produce the same toxines which they produce when growing within the body, and by which they set up the particular diseased state. There is, however, this great difference in this respect, that when multiplying within the body the amount of the specific chemical poison can reach, *cæteris paribus*, fatal proportions, whereas when multiplying in an artificial medium the nature and amount of this poison is subject to determinable conditions. But not only do pathogenic bacteria produce chemical substances acting like poisons, since other bacteria not capable of multiplying within the body can, as has been mentioned already, outside the animal system produce chemical substances, ptomaines, which act like poisons, and which when introduced into an animal body cause definite pathological states.

Since Gaspard, Virchow, Panum, and Bergmann have shown that various animal materials, blood and tissues, having undergone putrefactive changes, contain substances which by purely chemical means can be separated from the bacteria that produced them, and which, when injected into the body of animals, produce, according to the amount injected, more or less severe disturbances, leading even to a fatal result. When injected in small quantities, very soon after (from a quarter to one hour) a rapid rise of the body temperature with shivering takes place, followed by gastro-intestinal disturbance, retching and vomiting, tenesmus and purging; pain in the abdomen, muscular contractions and spasms; in large doses congestion and hæmorrhage occur in the stomach and intestines, particularly the duodenum and rectum, the peritoneum and the pleura; sanguineous and fluid evacuations pass from the bowels; a rapid fall of the body temperature, collapse, and death takes place. On *post-mortem* examination congestion is found in all the viscera and the serous membranes, hæmorrhages in the lungs and liver, in the serous and mucous coat of the stomach, the duodenum and rectum. The disturbance, or set of disturbances, called *sepsis*, *septic intoxication*, or *sapræmia*, takes place a short time after the injection; they are therefore caused by chemical poisoning, as is also proved by the fact that the substances injected are separated from the putrid materials by means which destroy and kill all living micro-organisms (precipitation by alcohol and boiling). Selmi has shown that the substances produced by putrefaction and causing the above *septic intoxication*, or *sapræmia*, possess certain well-defined chemical characters which show them to be alkaloids, and he called them *ptomaines*. Brieger isolated and more accurately defined these substances (*see* also Dr. Hunter's researches), and showed their production to be dependent on certain materials; he obtained them in crystallised form and showed that some, e.g. neurine, act very poisonously, while others (choline obtained from yolk of egg) do not do so. Hueppe obtained some ptomaine (cadaverine) of a very poisonous nature by cultivating Finkler's and Koch's spirilla in egg anaërobically. Various forms of toxic disturbances similar to the above have been observed to follow the ingestion of certain substances, as cream, cheese, pork and ham, sausages, mackerel, and other foodstuffs, and in all these the presence of ptomaines, as causing the severe gastro-enteritic disturbances followed sometimes by collapse and death, is also assumed. In most of these cases it has been shown that the intensity of the disturbance is proportional to the amount of the material consumed, and further that the symptoms set in very soon after the introduction of the material, so that there can be no doubt that we have to deal here with poisoning by chemical substances as opposed to infection with living micro-organisms, in which latter case there is always a considerable lapse of time or incubation period before the symptoms supervene, owing of course to the fact that in this case the micro-organisms must first multiply to a certain degree in order to produce the toxines, and by these the pathological results. But because the symptoms of the intoxication are very similar in all these cases—gastro-enteritic disturbances, retching and vomiting, tenesmus and diarrhœa, congestion and hæmorrhage of the internal viscera, even leading to collapse and death—it would be unwarranted to assume that they are all caused by the same chemical poison. Septic intoxication or sapræmia is no doubt produced by ptomaines—Selmi's and Brieger's ptomaines (*see* a former page)—the result of putrefaction, if these ptomaines are introduced by injection into the subcutaneous tissue or directly into the vascular system, but we are not aware that anyone has succeeded in producing it by simple ingestion; whereas the poisoning produced by certain articles of food has always followed ingestion. It is probably correct to assume that, besides the putrefactive changes, other similar, but by no means identical, changes brought about by micro-organisms occur, by which certain chemical poisons—possibly alkaloids—are produced, which, though similar to the ptomaines of putrefaction, are not identical with them. By putrefaction is generally understood a set of changes due to the multiplication of certain micro-organisms in albuminous materials, in the course of which albumen is peptonised, then further split up, yielding leucin and tyrosin, and also indol, with the simultaneous evolution of ammonia and sulphuretted hydrogen, &c.; in these processes, conspicuous by the evolution of ammonia, sulphuretted hydrogen, and indol, the ptomaines of Selmi and Brieger are produced. But there are a number of micro-organisms known, which do not cause in albuminous substances the typical putrefactive changes in the above sense. There is never any ill smell evolved, and no ammonia or sulphuretted hydrogen, yet very poisonous substances are produced. Take, for instance, the bacillus enteritidis of Gärtner, and the bacillus isolated by Gaffky from sausage; in one instance horseflesh, in the other sausages, produced severe gastro-enteritic disturbance. The writer has isolated several species of bacilli, one from veal pie that had caused in some members of a family gastro-enteritic poisoning, another from pork pie of a similar poisonous nature, and still another from beef pie. These bacilli when grown in broth or in nutrient gelatine produced poisonous chemical substances, as was proved by ingestion of the cultures into mice, in which severe gastro-enteritis and death were caused; no bad smell of any kind was noticeable in the culture-fluids; on the contrary, there was present in them a rather pleasant aromatic smell. Neither of the above bacilli is capable of growing and multiplying in the animal body, but when grown in broth or in gelatine they produce those poisonous substances. In some cases of poisoning by cream and cheese, Dr. Vaughan has isolated from such cream and cheese, crystals of a certain substance (tyrotoxin) which acted very poisonously. It follows, then, that the term ptomaine poisoning or sapræmia should be reserved for that set of cases in which the ptomaines of Selmi and Brieger, produced by putrefaction of albumen, are at play, while those special changes caused by special, non-putrefactive microbes in certain albuminous substances—e.g. cheese, mackerel, veal pie, sausage, pork, tinned meat of one kind or another—should be considered as special fermentative changes in no way similar to putrefaction, and the products of such fermentative changes should be, as is becoming more and more the custom, placed under the same group of toxins as are produced by the true pathogenic microbes.

Different from these intoxications, produced by chemical substances elaborated by bacteria outside the animal body, are the *true infective processes*. In these latter the microbes enter the system, multiply therein, and when sufficiently numerous, i.e. when their special toxins have been produced in sufficient quantity, set up a particular diseased state. The time that elapses between their entrance and the setting in of the symptoms is, as is well known, spoken of as the *incubation period*. In the true infective processes, then, there is an incubation period. The length of this is, as is also well known, different in the different diseases, and it marks one of the characteristics of the particular disease. But in the same disease it is subject to more or less marked variations, depending on the number of microbes introduced, on the susceptibility of the individual, and on other conditions not yet understood. It has been shown by the observations of Wyssokowitsch, W. Cheyne, and others that, within certain limits, the number of microbes introduced influences the length of the incubation period and even the severity of the disease, but beyond a certain number of microbes introduced no influence is noticeable. In some cases of very great susceptibility, e.g. rodents towards anthrax, pigeons, fowls, and rabbits towards fowl cholera, the influence exerted on the duration and severity of the disease by the number of bacilli originally introduced is very slight or almost nil, while in other diseases it is very marked, as in certain septicæmic disorders, e.g. malignant œdema and swine erysipelas. Here, when small numbers are introduced, the incubation period becomes very prolonged; in malignant œdema this prolongation is sometimes very considerable, and the disease is mild. The writer has seen in several cases of septicæmic infections (guineapig's septicæmia caused by a bacillus, the microbe of grouse disease, the bacillus of pneumonia, Middlesbrough) the incubation period vary, according to the amount injected, between twelve hours and two to four days, whereas in the case of the bacillus of fowl cholera even small quantities act like large doses, no change in the incubation period being noticed. It is feasible to assume that in those cases of slight susceptibility, where considerable quantities are required in order to produce the disease, this is due to the fact that the blood or the tissues have a certain killing power on a certain number of microbes (*see* the experiments of Niessen, Buchner, Lubarsch, and others previously mentioned), which killing power becomes, however, exhausted beyond that number of microbes. If, then, more than this number be introduced the surplus will survive, multiply, and cause the disease; if below this number, no living microbes remain and no disease is produced.

The coincidence of minor severity with prolonged incubation noticed in some, though by no means in all, cases of infections is a very curious phenomenon, and may possibly be due to the fact that in these cases a small number of microbes being introduced, they by gradual multiplication produce only sparingly the chemical poison, so that the animal body has time to accommodate itself, as it were, to the action of these toxins; and, further, that, owing to the small number of bacteria introduced, the incubation period becomes prolonged, the total amount of the toxins small, and the disease itself of a mild type. It is different if at the outset a large number of microbes be introduced; by the multiplication of these at once a large host and a large amount of toxins is produced, and the body not having time to accommodate itself, being as it were suddenly overtaken by these poisons, rapidly manifests the reaction and in a more striking and severe form.

CHAPTER X

MANNER OF INFECTION OR CONTAGION

The way in which the microbes or contagia enter an individual is subject to considerable differences, differences depending on the conditions of the surroundings as well as on certain conditions of the subject. While in some diseases the contagium enters the body by inoculation, i.e. through an abrasion, wound, or the like in the skin or mucous membranes; such as surgical septicæmia, traumatic erysipelas, tetanus, hydrophobia, malignant pustule, glanders; in others the alimentary canal or respiratory organs or both are the portals, though artificially also by inoculation the disease can be readily produced. Take for instance anthrax in sheep and cattle; this under natural conditions is always contracted by these animals through the spores of anthrax gaining access to the alimentary canal or respiratory tract; in woolsorters' disease also by the alimentary or respiratory tract; in small-pox, typhus, scarlet fever, measles, foot-and-mouth disease, diphtheria, tuberculosis, actinomycosis by the respiratory or alimentary canal;[1] in typhoid fever and in cholera by the alimentary canal; in relapsing fever and malarial fever by the respiratory organs. That in cases like scarlet fever, diphtheria, tuberculosis, typhoid fever, foot-and-mouth disease, cholera, dysentery, and others, infection takes place by ingestion of the contagium by articles of food—water, milk, fruit, and other materials—is well established. The division of bacteria into *ectogenic* and *endogenic*, first introduced by v. Naegeli, is accepted by many bacteriologists. Ectogenic are those pathogenic bacteria which are capable of living and thriving outside, and independent of the animal or human body, while endogenic are those pathogenic microbes which can only thrive in the living animal body: the former, though capable of carrying on life as saprophytes, can also exist in the living animal body as parasites producing a specific disease, while the latter exist only as parasites. Thus, to quote a few examples, the malarial microbe (plasmodium), the anthrax bacillus, various septicæmic microbes, e.g. of malignant œdema, the bacillus of typhoid fever, of cholera, of fowl cholera, fowl enteritis, swine fever, swine erysipelas, tetanus, human erysipelas, and a host of others, are all ectogenic; while the undiscovered microbe of small-pox and vaccinia, the undiscovered microbe of rabies, the microbe of leprosy, and that of syphilis, are endogenic. It is well known that rabies, syphilis, gonorrhœa, and vaccinia have never been known to occur other than by direct contact, the virus being transferred directly from one individual to another. While for general practical purposes this distinction into ectogenic and endogenic contagia may be admitted, nevertheless, when looked at from a theoretical and scientific point of view, its correctness becomes doubtful. Take, for instance, gonorrhœa: there is every indication that, as in syphilis, so also in gonorrhœa the microbe is ordinarily only of parasitic nature; but since it, i.e. the gonococcus, can be, and has been cultivated in artificial cultures, i.e. outside the human body, there is no reason whatever to assume that it cannot also carry on existence independent of the human body. Or take tuberculosis. Here also the microbe, i.e. the bacillus tuberculosis, is, as a rule, of the nature of a parasite, which, though it can grow well in certain artificial media independent of the animal body, does not, under natural conditions, carry on an independent existence: this is due to the fact that the bacillus tuberculosis being so highly specialised requires special media, and special temperatures, to carry on existence, conditions not met with ordinarily in nature. But Schottelius has shown ('Centralbl. f. Bact. und Parasit.,' VII., No. 9) that tubercle bacilli taken from the lung of phthisical bodies buried for years still possess the characteristic reaction, and are capable of producing tuberculosis on inoculation. This would mean that the tubercle bacillus, even after years, was still living and capable of carrying on an existence outside the *living* human or animal body, and, therefore, is not strictly endogenic.

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[1] Karkanoff made experiments on rodents with the bacilli of fowl cholera, and found that with these, infection is producible by ingestion, with anthrax very rarely, and with Emmerich's Naples bacillus not at all. He thinks that, as regards anthrax, infection probably takes place principally by way of the respiratory organs.

Of the same doubtful nature is the classification into fixed and miasmatic contagia. In former years this distinction was much used in practice; the first name 'fixed contagia' was meant to denote those contagia which in the narrower sense of the word act by contact, i.e. where the virus passes from the sick directly to the healthy, while the latter name 'miasmatic' indicated that the virus spreads not by direct contact but is volatile, i.e. communicates itself to the air, and thence finds entrance into a new individual. Those contagia were considered as a third group, which in some cases proved themselves to be either fixed or miasmatic, i.e. in some cases act by direct contact, in others by the air. But since the contagia have been proved to be of the nature of minute microscopic particulate matter, some of which can easily become distributed through the air in a living and active state, the above distinction has lost somewhat of its scientific basis. Take, for instance, anthrax: this would certainly be considered as a fixed contagium, i.e. the anthrax bacilli contained in any material derived from an animal dead of anthrax; and yet we now know that the spores of bacillus anthracis when adhering to dry material can easily become distributed through the air and produce infection, e.g. woolsorters' disease. Or take diphtheria: this was always considered to be a disease in which the contagium is typically a 'fixed' one; yet why the diphtheria bacillus, or particles of matter enclosing the diphtheria bacillus, when protected from drying and dying, should not be able to become distributed through the air, there is no theoretical reason whatever. As a matter of fact, some health officers ascribe to sewer air, in localities in which diphtheria cases had been prevalent, the power to convey to the healthy the contagium of diphtheria. That diphtheria can be, and often is, communicated through infected milk, there can be no manner of doubt, and there can be no theoretical reason adduced why the diphtheria bacillus enclosed in and guarded by albuminous or other matter from drying up (the diphtheria bacillus does not form spores, and is killed by thorough drying) should not be able to produce infection through the air into which it had become distributed. From a practical point of view, it is perfectly true that vaccinia, rabies, tetanus, glanders, and syphilis are not communicated by the medium of air, but by direct contact, i.e. their contagia are fixed, and it is equally true that malaria and relapsing fever are naturally communicated as miasmatic contagia; but when we come to anthrax, variola, tuberculosis, erysipelas, pneumonia, fowl cholera, swine fever, and many others, the distinction breaks down, and we have then to speak of contagio-miasmatic diseases.

An important point in the method of infection is the question, whether microbes can pass the uninjured mucous membranes. The opinions of pathologists are divided: some maintain that such is the case, while others doubt it. Those who are for such a passage of the bacteria into the uninjured membrane rely on the fact ascertained in numerous cases, that certain diseases (small-pox, syphilis, tubercle) have been transmitted by the mother (in human beings and in animals) to the fœtus in utero, while those who doubt the passage of bacteria through the uninjured membranes rely on the fact that in equally numerous cases, equally well established, such a transmission did not take place. Now it must not be omitted, in judging of this question, to bear in mind that the individual cases in which the disease was or was not transmitted by the mother to the fœtus must be judged by themselves. For instance, there have been cases described, in which in cattle anthrax has been certainly transmitted by the mother to the fœtus; but here it must be remembered that ruptures of small vessels in different organs (lung, intestine, kidney) is of a common occurrence in an animal affected with malignant anthrax, and there is no reason why such ruptures of vessels and hæmorrhage should not occasionally occur also in the placenta. The blood of such an animal, containing the bacillus anthracis, could in these cases of ruptures in the placenta easily get into the vascular system of the fœtus; all one has to suppose is that some of the capillaries of the fœtal placenta, at one or the other point of hæmorrhage in the maternal placenta, might also have been involved in the process of destruction by pressure or otherwise. In such a case the bacilli might easily pass into the vessels of the fœtal placenta, and further into the fœtal circulation, and here set up anthrax. On the other hand, the placenta of the mother might remain uninjured, and in such a case no bacilli would penetrate from the mother into the fœtus, which would escape anthrax though the mother died of it. The writer has in several instances had the opportunity of dissecting guineapigs and mice that had died (after inoculation) of virulent anthrax; there were present in these animals several fœtuses, whose blood and spleen were carefully examined for the bacilli anthracis, both with the microscope and by culture, yet no bacilli could be discovered in the fœtus. Sections through the whole placenta (maternal and fœtal) showed very clearly that the bacilli anthracis, though abundant in the vessels of the maternal portion, stopped short of the vessels of the fœtal placenta; in fact, there could be seen a sharp line of demarcation between the maternal vessels containing the bacilli and those of the fœtal vessels free from them.

Lingard has shown for anthrax ('Proceedings of the Royal Society,' 1889) that it is possible to inoculate with anthrax the fœtus in utero of the rabbit, without the disease being communicated by the fœtus to the mother; in these instances the blood of the fœtus swarmed with anthrax bacilli, and the fœtus of course died of anthrax, yet the mother remained free of anthrax, thus proving that the bacilli did not pass from the vessels of the fœtal placenta into those of the mother. Although hereditary tuberculosis of the offspring is notoriously a common occurrence, tuberculosis of the mother need not necessarily always be communicated to the fœtus, though in cases of experimental tuberculosis in the guineapig, tuberculosis in the fœtus may be and has been occasionally found: this notably occurs when tubercles are present in the placenta.

But although the passage of microbes from the maternal circulation into that of the fœtus does or does not occur according as the placental vessels are or are not involved in the disease, there can be no doubt that microbes can pass through the wall of the intestine and become absorbed into the system: this is the case in mycosis intestinalis; i.e. anthrax starting from the intestinal canal; in primary intestinal tuberculosis, in tabes mesenterica, and other diseases. Besides, since many infectious diseases have their portals in the lungs (small-pox, measles, tuberculosis, typhus, woolsorters' disease, pneumonia, ragsorters' disease), it is clear that a passage of the specific microbes through the walls of the alveoli is in these instances a notorious occurrence. Similarly, microbes using the alimentary canal as a portal must be capable of becoming absorbed from the intestinal canal; for instance, in milk scarlatina, and in typhoid fever, such must be of normal occurrence. A further important question is how far the microbes can pass unscathed the influence of the gastric juice. The acidity of the gastric juice (0·2 per cent.) is sufficient to kill in a few minutes some species of bacteria which are non-spore-bearing, but it is doubtful whether in all cases and under all circumstances such an effect is exerted or is produced. To quote a few instances only. The bacillus prodigiosus (micrococcus prodigiosus) is a non-spore-bearing microbe, and yet readily passes the stomach in a living state. When added to the food of animals there is no difficulty in demonstrating it, a few hours after, in the contents of the small intestine: the bacillus of pneumonia (Middlesbrough) is a non-spore-bearing bacillus, but there is no difficulty in infecting mice with it, if mixed with the food; the micrococcus scarlatinæ is non-spore-bearing, but the writer has proved that, by adding it to the food of mice, these animals become infected and die; the bacillus of fowl cholera and of fowl enteritis is non-spore-bearing, yet under natural conditions the alimentary canal is the portal of entrance, the animals picking up the contagium with their food from the tainted soil; and there are other similar cases. In all these instances, then, though the microbes are non-spore-bearing, they escape the action of the gastric juice, pass into the intestine in a living state, become absorbed, and produce infection. On the other hand, it has been proved that anthrax bacilli in the non-spore-bearing state do not produce infection when administered with the food, while spores of the anthrax bacilli have been shown to pass unscathed through the stomach, and in some cases have been capable of setting up malignant anthrax (Falk, Koch, Gaffky, and others). Indeed, under natural conditions, we must suppose that when sheep or cattle, grazing and sojourning on infected soil, contract infection with anthrax, they contract it by spores which, having entered into the stomach with the food, have thence passed unscathed into the small intestine, and by becoming absorbed have set up the disease. But this does not apply to all animals and to all cases (Koch, Buchart, and others), since in many experiments, e.g. on mice, ingestion of spores of anthrax bacilli has failed to produce fatal anthrax, while in other cases (Falk, Koch, and Gaffky) it certainly has been followed by positive results. The spirillum of Asiatic cholera is a non-spore-bearing microbe; it is killed on exposure for a few minutes to the action of hydrochloric acid of 0·2 per cent. (Koch, Watson Cheyne); yet Macfadyean has shown that when the microbes are administered with the food (milk) to dogs, they pass unscathed through the stomach, while with water they do not do so. Koch and others have shown that when this microbe is administered with the food to the guineapig, it does not pass unscathed through the stomach, unless the contents of this organ be previously made neutral or alkaline (*see* a further chapter). There can then be no doubt about the fact that the gastric juice has an inimical effect on many non-spore-bearing microbes, but it does not follow—indeed, experience disproves it—that under all conditions non-spore-bearing microbes are killed in their passage through the stomach. Whether the cause for this is to be found in particles of the contents of the stomach not becoming sufficiently exposed to the action of the gastric juice, or in the condition of the gastric juice itself—not always being of the same degree of acidity—or to both, or to some other condition, is undecided; the fact remains that non-spore-bearing microbes administered with the food do in some instances pass unscathed through the stomach, spore-bearing ones easier and oftener. The tubercle bacilli, which as experiment proves are spore-bearing, pass always unscathed through the stomach, and produce tuberculosis of the intestine. Anthrax spores often pass and set up malignant fatal anthrax.

CHAPTER XI

DISINFECTION

In the foregoing chapters we have mentioned various agencies which, though not destructive of the life, are nevertheless inimical to the growth and multiplication of bacteria; and further, other conditions which are capable of altogether destroying their life. We will now proceed to systematically consider these agencies. We may subdivide them into two great categories, just indicated, viz. influences which inhibit the growth and multiplication of bacteria, these are called restraining influences; and those that altogether annihilate the life, these are called killing influences.

A. Restraining Influences

As such are to be regarded (*a*) temperatures below 12 to 14° C. and above 40 to 42° C. It will be, however, remembered that we mentioned several species which can well exist and multiply below 12 or 14° C., e.g. some water bacteria, and bacteria in the soil; while others, e.g. bacillus thermophylus, grow well at temperatures far above 42° C. There exist some species on which temperatures above 25° C. have a restraining power, e.g. bacillus prodigiosus, the bacillus of veal pie, and a spore-forming bacillus of dust; then there are other species on which a temperature below 25° C. has a restraining power, e.g. a streptococcus of the fluid of the mouth, the streptococcus of Schütz, causing infectious pharyngeal abscess in the horse, the diplococcus pneumoniæ, and the tubercle and leprosy bacilli.

These restraining influences of certain temperatures do not possess any direct killing effect on these several bacteria.

(*b*) *Moisture.*—Absence of sufficient moisture is in itself a powerful restraining agency, for no growth can take place if the amount of moisture is insufficient. In a dry atmosphere or under conditions causing dryness or absorption of much moisture, e.g. caustic potash or soda, quicklime, or sulphuric acid, kept side by side with the culture medium in a closed space, no growth takes place.

(*c*) *Light.*—Diffuse daylight and sunlight have a restraining power on some species more than on others, for all bacteria grow best in the dark. Direct sunlight has, as has been mentioned, a powerful killing power.

(*d*) *Unfavourable Soil.*—Acidity of the soil is a powerful restraining influence; in many cases, if strongly acid, exerting a killing influence on non-spore-bearing bacteria. Strong alkalinity of the medium is likewise a restraining condition. The presence or absence of certain substances, as we have seen, is a powerful influence: e.g. the presence of sugar is unfavourable to some bacteria, while it favours others; the presence of minute traces of phenol, of perchloride of mercury, of iodine, the absence of sodium and potassium salts, and particularly the absence of sufficient proteid material, have each a powerful restraining influence on many species; the presence and accumulation of the chemical products, a result of the multiplication of the bacteria themselves, have a restraining influence; the presence of various substances such as occur in fæcal matter acts injuriously on the multiplication of some bacteria; the presence of other more vigorously growing bacteria interferes with the growth and multiplication of some less vigorous bacteria. Examples of this kind have been mentioned in a former chapter, as also the influence of putrefaction on some pathogenic bacteria.

The methods for testing the restraining power of carbolic acid, perchloride of mercury, and others are briefly these: The disinfectant is mixed with nutrient broth or nutrient gelatine in definite proportions; this mixture is then inoculated with a trace of the bacterial culture in the ordinary manner, and on incubation the result is watched, viz. whether no growth appears, whether the growth is normal both as to time, aspect, and amount, or whether it is retarded, different in character, and less in amount.

Carbolic acid added to the nutritive medium in the proportion of 1 in 400 to 500 has a decided restraining power; perchloride of mercury added

1 : 20,000–50,000 has a restraining power on some (bacillus anthracis, bacillus mallei, streptococcus scarlatinæ), while it has no restraining power in these proportions on others (bacillus subtilis, spirillum of Finkler and Koch, staphylococcus pyogenes aureus, bacillus prodigiosus, streptococcus pyogenes, and some others). In these latter cases the amount of perchloride required is 1 : 10,000, or even greater.

B. Killing Influences

(*a*) *Temperature.*—It has been mentioned that with few exceptions in all non-spore-bearing forms of bacteria exposure to a high temperature, such as 75° C., 70° C., 60° C., or even 58° C., for several minutes [70° C. for one minute, 58° C. for 5 to 10 minutes] kills the bacteria; further that the spore-containing bacilli and the free spores withstand considerably higher degrees of temperature. Between the very resistant spores found in some tinned food-stuffs by Cohn not killed by exposure to the temperature of boiling water for half an hour, and the spores of bacillus anthracis killed by boiling in from one half to one minute, there exist all intermediate degrees of resistance. Thus, for instance, the spores of hay bacillus must be kept in boiling water for six minutes before they are killed with certainty; the spores of the Jequirity bacillus do not survive boiling for seven minutes; the spores of the bacillus filamentosus of sewage are killed by five minutes' boiling; the spores of the scurf bacillus and of some potato bacilli just escape being killed by five minutes' boiling.

As regards the killing power of the temperature of 100° C., i.e. of boiling water, it has been shown by Koch and others that flowing steam, i.e. steam in movement, is the most efficient, dry heat the least efficient. Dr. Parsons's report to the Medical Officer of the Local Government Board in 1886 on Disinfection by Heat gives a full account of the means employed and the results obtained. The spores dried on silk threads previously sterilised, or on bits of calico or flannel previously sterilised, are exposed directly to the high temperature, and with them inoculation is made of broth tubes or of gelatine plates and the result watched. Or, in order to test their resistance to boiling water, sterile broth is inoculated with the spores from a pure culture, and this broth tube is then exposed to the temperature of boiling water (over the flame) for the desired time. If the influence of water of any given degree up to 100° C. is to be tested on bacteria or their spores, broth tubes are inoculated with the culture and exposed to the desired temperature in an apparatus which is described in the report of the Medical Officer of the Local Government Board for 1889. The writer has found it easy to keep the temperature of the water in the apparatus constant by a small flame of the Bunsen burner; alterations of quarter to half a degree Centigrade are the utmost differences noticeable. The temperature of the broth in the test tubes is, as a rule, equalised within half a minute to about half a degree Centigrade, so that if it is desired to expose the broth in the test tubes to, say, 60° C., the temperature of the water in the apparatus is kept at 60 to 60·5° C. When the tubes have been kept in the water for the desired period they are taken out and at once placed in cold water, so as to immediately stop any further influence. Just like broth tubes, gelatine tubes can also be heated, and then with these plate cultivations can be made. Owing to the great resistance of spores to high temperature, differentiation of spores from a mixture of bacteria can be easily made by heating the mixture up to 80–90° C., for all bacteria except the spores are hereby killed without fail, the spores remaining alive. For example, if a culture containing spores of hay bacillus, that happens to be contaminated by micrococci and non-spore-bearing bacilli, be heated to a temperature of 80 to 90° C. and then from it fresh broth or gelatine be inoculated—as tubes or as plate cultivations—the result will be pure cultures of the hay bacillus only.

(*b*) *Drying.*—By thorough and complete drying, all bacteria are killed, except spore-bearing ones and the spores themselves. The spores of all the known species resist drying for indefinite periods. The writer has kept the spores of various potato bacilli, of bacillus anthracis, of hay bacillus, of scurf bacillus and of Jequirity bacillus, contained in agar tubes, in a perfectly dry state, i.e. the tubes were kept in a closed desiccator over sulphuric acid till the agar covered by the culture had dried up into a thin shrivelled film:—and yet even after two years and a half on inoculating fresh materials from the above tubes typical and good growths were obtained. Non-spore-containing bacteria, e.g. various species of staphylococci, various species of streptococci, bacilli of typhoid fever, of swine fever and swine erysipelas, Koch's and Finkler's spirilla, bacilli of pneumonia, bacilli of fowl enteritis and fowl cholera, of grouse disease, as well as a number of other species of bacteria, were kept—as agar cultures—in the incubator till these latter had well dried up; no sub-cultures could then be raised from any of them. On drying non-spore-bearing bacteria over sulphuric acid, in a brisk current of air, or simply placing a very thin film on cover-glasses in the manner employed by Koch and leaving them till dry, such as the bacillus anthracis of the blood or spleen, Koch's or Finkler's spirilla, the bacillus of typhoid fever, staphylococci or streptococci, bacillus of swine erysipelas or swine fever, bacillus of pneumoniæ (Middlesbrough), bacillus of fowl enteritis and fowl cholera, and many others, and then placing these cover-glasses in broth or on gelatine and incubating them, no growth of the above bacteria takes place. If the drying is not complete, that is, if the film be too thick, so that the superficial layer forms a protecting crust for the rest, then the result of inoculation with such material will be positive; the bacteria in the depth, having been protected against drying, survive, and can produce a new crop. Similarly when particles of solids containing bacteria are dried, it will be found that here also the centre escapes thorough drying, being protected by a superficial crust. Ordinary dust particles, however small, are never so dry that the bacteria contained in them are killed. The proof of this is, that numerous species of non-spore-bearing bacilli and of micrococci can be cultivated from dust, be it dust floating in the air as motes visible to the eye only by Tyndall's searching beam of light, or be it dust of a floor or of the wall of a room, or on any other object.

(*c*) *Light.*—The disinfecting power of the direct sunlight has been mentioned above.

(*d*) *Chemical Disinfection.*—Koch, his pupils, and others have tested a variety of substances, such as alcohol, iodine, lime, carbolic acid, sulphate of iron, permanganate of potassium, tar, arsenic, perchloride of mercury, and others. As is obvious, according to the nature of the bacteria, according to the strength of the solution and the time of exposure, the result will be found different: for example, bacilli anthracis of the blood, i.e. sporeless bacilli, are killed by 5 per cent. carbolic acid in five minutes, but they are not injured by 1 per cent. carbolic acid in five minutes. Bacilli anthracis of the blood are killed by 1 : 20,000 perchloride of mercury after ten minutes' exposure, but remain uninjured after five minutes' exposure.

The methods used most efficiently for testing the killing power of any reagent are these: (*a*) exposure of the bacteria to the reagent in solution; either by mixing a trace of the culture with a comparatively large amount of the reagent, or by placing in the reagent silk threads, a piece of blotting-paper, or other similar material previously charged with the culture, and then inoculating with a trace from this about 8 to 10 c.c. of sterile broth, contained in a test-tube, and exposing this to a temperature of from 35 to 37° C., or making plate cultivations in gelatine.

If growth appears, note the rapidity and character of the growth as compared with control tubes, i.e. tubes inoculated with the non-medicated bacteria; if doubtful whether the growth is of the right character and pure, make fresh plate cultivations.

(β) If the bacteria possess definite pathogenic power, inject, after exposure to the reagent, a small quantity of the medicated culture into a suitable animal and watch the result. We will illustrate this by giving three examples: (1) Koch's cholera spirilla; (2) anthrax bacillus of blood; and (3) spores of bacillus anthracis.

(1) *Koch's Cholera Spirilla.*—From an active culture a droplet is mixed with the disinfectant, contained in a test-tube plugged with cotton wool, or in a sterilised watch-glass covered up with another watch-glass; after the lapse of the desired time, by means of the capillary pipette or the platinum hook inoculation is made from the mixture into a broth tube containing about 8–10 c.c. and into a gelatine tube; the former is placed in the incubator at 35–37° C., the latter is melted, shaken, and a plate cultivation is made. If the broth remains clear after forty-eight hours' and longer incubation, and if no characteristic colonies appear in the plate, the spirilla have been killed by the disinfectant.

(2) A droplet of blood of the heart or spleen of an animal dead of anthrax is mixed as above with the disinfectant; after the lapse of a certain time inoculation is made of broth tubes, of gelatine tubes for plate cultivation, of gelatine tubes in stab cultures, and at the same time a guineapig is inoculated with several drops of the mixture. If the bacilli have been killed by the disinfectant, none of the tubes and plates will show the characteristic growth of the bacilli anthracis, and the animal remains perfectly normal; but if the bacilli have not been killed, either of two results follow: (*a*) either the tubes show normal growth in the normal time, and the animal succumbs to anthrax in the normal time—thirty-six hours to three days—or (*b*) the growth resulting on inoculation is retarded and smaller in amount, and the animal though showing swelling at the seat of inoculation does not die of anthrax, or dies after a prolonged period (six, seven, or even nine days). In the latter case the bacilli have evidently been injured though not killed by the disinfectant.

(3) A trace of spores—from an agar or broth culture, or from a potato culture—is dried on silk threads, and these are then placed in a solution of the disinfectant for a stated time and then placed in broth or gelatine; or a trace of the spore material is mixed as above in a test-tube or watch-glass with the disinfectant. The testing of the effect is carried out as in (2).

Of all disinfectants hitherto examined, perchloride of mercury solution deserves the first place as a thorough disinfectant, for a solution of 1 : 500 (one grain to about one ounce of water) applied to any material containing spores of even the most resisting kind, e.g. those of hay bacillus, or of tubercle bacilli, sterilises the spores after an application not lasting more than a minute; one in a thousand sterilises most though not all spores when acting from five to ten minutes; one in five thousand kills all non-spore-bearing forms with certainty, even after one-half to one minute's immersion. In the application of perchloride of mercury as of all those agencies which have an affinity to proteids either by coagulating them, as, for instance, alcohol, and perchloride of mercury, or by oxidising them, e.g. sulphate of iron, and permanganate of potassium, or by decomposing them like chlorinated lime—it must be borne in mind that if any material containing proteids is to be subjected to disinfection, the disinfectant must be added in considerable excess in order to make allowance for the waste necessary in the action on the proteids themselves, so that sufficient of the active disinfectant remains to kill the bacteria. Thus, for instance, in the case of typhoid stools, cholera stools, tubercular sputum, sputum of croupous pneumonia, &c., a considerable excess of the disinfectant must be added, whereas in experiments with pure cultures, taking of these a trace only, the excess need not be so great.

Besides perchloride of mercury, 5 to 10 per cent. carbolic acid, chlorinated lime,[1] iodoform, iodine, bromine, tar (1 per cent.), and lime, are good disinfectants. With this latter the writer has had occasion to make a considerable number of experiments to test its disinfecting power on various bacteria, both as lime milk and as lime with herring brine (the amine process). In the latter case, viz. lime and brine, the amount of lime is effective in smaller proportions than when lime alone is used. Seventy grains of lime and six grains of herring brine to the gallon of water are mixed and then immediately added to the fluid which is to be disinfected; a voluminous precipitate is formed, which soon settles to the bottom of the vessel; while the supernatant liquid is clear and practically sterile. In the case of non-spore-bearing microbes the precipitate is not quite sterile, but the living microbes become in a few days reduced to a large extent.

In the case of sewage the amine treatment yields a practically sterile effluent, and in the sludge the number of surviving microbes diminishes from day to day. The effect of milk of lime has been tested for comparison on a good many species of bacteria, and its disinfecting power when used in the same proportion of strength was found to be considerably less.

SECTION B

CHAPTER XII

SPECIFIC OR PATHOGENIC BACTERIA

Suppuration and Acute Phlegmon.—Acute phlegmon is a disturbance of the connective tissue initiated by vascular alteration. This alteration manifests itself in engorgement; the arteries, capillaries, and veins are dilated and filled with blood, the circulation in the arteries, capillaries, and veins is at first accelerated, then it becomes slower in the capillaries and veins, and the blood in some of these ultimately undergoes stasis. These changes have been observed under the microscope by Cohnheim, and have been graphically described by him in Virchow's 'Archiv,' Band XL. At the same time diapedesis of red corpuscles (in capillaries), particularly emigration of white blood-corpuscles (in capillaries and veins) and exudation of plasma (in arteries and veins), occur, whereby the connective tissue of these parts becomes swollen, the bundles more or less separated one from another, and the lymph-spaces of the connective tissue filled with plasma, red and particularly white corpuscles. As the process continues the matrix of the connective tissue undergoes retrograde changes, both in its fibrous matrix and in the connective tissue corpuscles: the fibrous matrix breaking down, many of the connective tissue corpuscles swelling up, becoming vacuolated, and ultimately degenerating; but active changes, enlargement and division of these are also maintained by some observers (Stricker and Norris). The increase of leucocytes or round cells in the connective tissue both by continued emigration as well as active division of those that have emigrated leads to the formation of at first small cells, then according to the size of the inflamed area to large accumulations of them: these are the pus-cells, which when localised form an abscess.

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[1] Nissen on chlorinated lime as disinfectant, *Zeitschr. f. Hygiene*, VIII. 1.

As this accumulation of leucocytes and plasma proceeds, the connective and other tissues around it become gradually involved in the process; the phlegmon and abscess enlarge at the expense of these tissues, and they themselves undergo degenerative changes and are broken down. In consequence of this, when in the skin or in mucous membranes the surface is gradually reached, the abscess discharges itself and an open sore or ulcer is established; then the process of granulation, healing, and cicatrisation commences from the tissue next to the base of the ulcer.

It is not our object to trace and describe all the details of the pathological changes going on in the connective and other tissues during this process of phlegmon, nor the localisation of the accumulation of leucocytes, as abscess, nor the ulceration and healing, but we will limit our description to their fundamental causes.

In all acute phlegmons, either of the nature of diffuse infiltration with much plasma and relatively few leucocytes (œdema), or with comparatively little plasma and many leucocytes (purulent inflammation and abscess), the leucocytes or round cells form the most conspicuous formed elements; as to other formed elements, notably the micro-organisms present, a clear insight can only be had if the inflammatory matter, exudation, or pus be taken from a phlegmon or abscess which is still removed from the free surface; for the matter taken from an exposed surface, such as an open sore of the skin or mucous membrane, or the exudation of the surface of an inflamed mucous membrane, as in catarrh, contains various species of microbes, as was mentioned in a former chapter, not necessarily connected with the diseased process; besides, an inflamed tissue, particularly one in which there is a good deal of breaking down of the tissue elements going on, is a suitable soil for the growth and multiplication of various kinds of saprophytes not having any relation to the disease.

In *acute abscess*, preparations made of the inflammatory matter or of the pus, taken from the depth, reveal in most cases micrococci (Ogston, Rosenbach) in variable numbers; they are found either singly or in dumb-bells, or even in short chains, or in smaller or larger clumps; as a rule, most are suspended in the plasma; here and there one sees them attached to the surface of a pus cell, or to the surface of a particle of *débris* or other elements not pus cells, e.g. epithelial or connective-tissue cells, muscle fibres, or connective-tissue bundles, &c., or one finds them enclosed within the substance of pus or other cells. In sections through phlegmonous tissue one sees them in more or less continuous masses pervading the tissue, in lymph-clefts and in blood-vessels in which stasis has occurred, particularly in the parts most disorganised. These micrococci stain readily by the ordinary methods, and when cultivations (streak cultures or plate cultivations) are made of such pus, either one of the following species, or sometimes two together, can be isolated in large numbers of colonies (*see* the literature on the subject by Rosenbach, Paltauf, Bonone, and others).

(1) *Staphylococcus pyogenes aureus liquescens.*—This is the most common species in acute purulent inflammation, and in sores following the discharge of abscess. As its name staphylococcus indicates, it forms by rapid multipli-

cation masses and aggregations; its colonies in gelatine, and particularly on agar, have a more or less yellowish-orange tint, and it rapidly liquefies gelatine. In gelatine plate cultivations the colonies appear on the second day as minute whitish yellow dots, which during the third day in transmitted light have a brownish tint, and are situated in a somewhat depressed pit, due to the gelatine surrounding it having become liquefied. During the fourth and fifth days the circular colony increases in size, and assumes in reflected light a more or less orange tint, the liquefaction has become considerable, forming a broad clear circular zone around the colony, which has sunk to the bottom of the liquefied zone, the zone of liquefied gelatine remaining clear and limpid. In stab culture in gelatine the stab is indicated as early as the second day as a line of whitish dots more or less closely placed together. Liquefaction begins from the upper part of the stab; during the third and fourth days the liquefaction is considerable, the droplet-like dots are deposited at the lower end of the channel of liquefaction, and are of a golden yellow colour, the liquefied gelatine being clear and limpid. In streak cultures on agar the streak is indicated by a broad band, smeary like paint, and of a golden yellow colour; the band rapidly increases in breadth, is moist looking, and its outline is more or less knobbed; after a few days (four to six) at 37° C. the band reaches its maximum growth, and its colour then gradually becomes paler, which change may go on till it is only just slightly yellowish tinted. In broth at 37° C. it grows very rapidly (*see* a former page) and produces strong uniform turbidity.

This micrococcus, as stated above, is very common in pus of acute abscess; it is present also in many other purulent inflammations, primary and secondary, acute osteo-myelitis, catarrhal inflammations of various kinds. There is one important addition to be made to what has been just stated as to its biological character, and that is that there exist several varieties of this microbe, slightly different one from another: the differences consist in the rapidity of the growth, in the rapidity of the liquefaction of the gelatine, and in the tint of the colour of the growth on nutrient agar. The writer has isolated from pus of acute traumatic abscess in the human subject a staphylococcus aureus liquescens, exactly like the one described above as the typical staphylococcus aureus liquescens; while from the pus in acute abscess of the udder of the cow a staphylococcus aureus liquescens was isolated, that grows more slowly than the former, which liquefies more slowly, and of which the colour on nutrient agar is less golden and fades more rapidly; then from infectious ulcer of the teats and udder of cows (Wiltshire disease), and from the infectious ulcer of the teats of cows affected with the Edinburgh disease, a staphylococcus aureus liquescens was isolated, which in all media except broth compares with the typical staphylococcus aureus; again, from opaque human vaccine a staphylococcus aureus liquescens was isolated, which behaved like the typical human staphylococcus aureus liquescens, except that it did not fade, and its colour on agar was and remained deep golden; from the blood of grouse dead of the grouse disease the writer obtained a staphylococcus aureus liquescens, which, though the same as the typical staphylococcus aureus liquescens of human pus in broth and gelatine, produced on agar only a faintly yellow tinted growth. Finally the writer has several times come across staphylococcus aureus (from blood, from air, from dust) which did not liquefy gelatine, but in all other respects was similar to the classical staphylococcus aureus.

The typical staphylococcus aureus liquescens of human pus and phlegmon, while recent, produces abscess and purulent phlegmon on inoculation under the skin of rabbits and guineapigs, but it gradually loses this power on continued sub-cultures; besides, the amount necessary to produce purulent inflammation must be always considerable. Bujwid ('Centralbl. f. Bact.,' 1889) has shown that the pyogenic power of this microbe is enhanced by simultaneous injection of a 12 per cent. sugar solution.

Occasionally inflammation and metastatic abscesses are produced in the rabbit in the lungs, in the pericardium and peritoneum, the liver and spleen by intravascular injection of large quantities of this organism. In all these localities the staphylococcus aureus liquescens can be demonstrated in cover-glass specimens and by cultivation. (For its relation to ulcerative endocarditis *see* a further page.)

Acute purulent abscess of the marrow of tubular bones in the rabbit has been produced by Becker on injecting the staphylococcus aureus liquescens, traumatic injuries of the bones having been previously established; hence it is probable that acute purulent osteo-myelitis also in the human subject is the result of an infection with the staphylococcus aureus liquescens.[1] The writer has made numerous experiments with some of the species of the staphylococcus aureus liquescens above mentioned, but has not been able to produce pathogenic results.

Duclaux and especially Heydenreich (St. Petersburg, 1888) describe the presence of staphylococcus aureus (or a variety of it) as the cause of the chronic purulent disease known as the 'Aleppo bubo' or the 'Pendje tumour;' tumours appear on the skin of the face and extremities, which in the course of a year soften into abscess, open, and then heal. Duclaux found the cocci even in the blood. Cultures of it injected into rabbits produced local gangrene, and in large doses septicæmic infection.

(2) *Staphylococcus pyogenes albus liquescens.*—This organism differs from the former only in the fact that its colonies on gelatine are, and remain, white in reflected light; on nutrient agar it forms a moist-looking whitish uncoloured film. Its power of liquefaction, and the rate of its growth, are the same as in the former. This staphylococcus albus liquescens is common in pus, both of acute abscess as also in various kinds of purulent matter; it is found in air, in dust, and in acute and chronic inflammations; it is also found in secondary inflammation, such as in purulent pyæmic inflammations in the joints, in the glands, in the serous membranes, in the lungs, following infectious diseases like small-pox, diphtheria, scarlet fever, and typhoid fever. In pus of acute abscess, and in purulent catarrhal inflammation (rhinal, bronchial, vaginal, urethral, conjunctival), it is easy to isolate this species by plate cultivation. When its culture is obtained from any purulent matter, and is subcutaneously inoculated in rabbits or guineapigs in sufficient quantities, it produces acute purulent inflammation, either as general diffuse purulent inflammation, at and about the seat of inoculation, or as localised abscess. By continued sub-culture it soon loses this pathogenic power. Several (one to two) cubic centimetres of a recent broth culture injected into a vein of a rabbit produce death in a few days by disseminated inflammation and abscesses in the viscera, in all of which the staphylococcus albus liquescens can be demonstrated by cover-glass specimens and culture. Acute septicæmic infection, and death in twenty-four to thirty-six hours, are occasionally produced in rabbits, the blood of the general circulation containing the microbes in large numbers.

(3) *Staphylococcus pyogenes albus non-liquescens* is another species, occasionally obtained from phlegmon and pus. As its name indicates, it

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[1] On the relation of staphylococcus aureus to osteo-myelitis, and the experimental production of the latter by intravenous injection of the former, *see* Rodet (*Revue de Chirurgie*, 1885), and particularly Lübbert (Würzburg, 1886).

is white in streak cultures on gelatine and agar, and it does not liquefy gelatine; it grows rapidly, but not so rapidly as either of the two previous ones; its colonies are more or less round whitish dots. Also of this there exist various species, differing from one another in some details, e.g. in rapidity of growth, in outline of streak cultures, and in size. In broth, the differences are more pronounced, since one produces more turbidity than another, one causes a greater precipitate than another, and one causes something like a pellicle, the others not. The staphylococcus albus non-liquescens is found in many other materials besides phlegmon and pus, e.g. occasionally in air, dust, and soil, in the secretions of the nose and fauces, also in drinking water and in sewage; from many putrid materials several varieties can be isolated.

Obtained from phlegmon, and inoculated into the subcutaneous tissue of rabbits and guineapigs, purulent inflammation follows in a certain percentage of cases, provided large quantities be injected.

(4) *Staphylococcus pyogenes cereus albus* (non-liquescens) and *staphylococcus pyogenes citreus* (non-liquescens).—The first differs from the previous one in that its colonies and its streak cultivation are of a waxy white appearance; the colonies grow in the course of a week or so into round flat patches, they are thin, flat, and more or less sharply outlined, more or less dry, and look like white wax. This is not often obtained from phlegmonous tissue. It is not unfrequently obtained from vaccine lymph. No result is obtained on inoculation into animals. The second of the two, as its name indicates, forms greenish yellow growths.

(5) *Streptococcus pyogenes* (Ogston, Rosenbach,[1] Krause, Passet).—This occurs frequently in acute phlegmon, though it is oftener found in the fluids and tissues of chronic purulent processes, in pneumonia, in necrotic and purulent matter of secondary infections: in abscess and necrosis of lymph glands, of the liver, in synovial and serous cavities following or associated with ulceration of the skin and mucous membranes. This microbe forms longer or shorter chains when grown in fluid media; on solid media the chains are not very pronounced. Its colonies grow slowly on gelatine; after two or three days they appear as whitish grey dots, which only gradually enlarge; on the surface they grow into irregularly outlined, more or less circular patches, thicker in the middle than at the periphery, which latter becomes gradually serrated or irregularly fringed; the colonies grow better on the surface than in the depth of the gelatine, where they remain small droplets. In stab cultures in gelatine the stab is indicated after two days as a grey or whitish line, which under the microscope is made up of closely placed minute droplets; in streak culture the line of inoculation is indicated after two to three days by a series of minute grey or white dots: these increase in size and number, as growth proceeds, but the streak is always made up of separate dots, which when closely placed become more or less fused one with another. After about a week's growth the streak and colonies are white when seen in reflected light, light brown in transmitted light.

The streptococcus pyogenes obtained from pus or fluid of acute phlegmon or of pus of chronic abscess forms fine long chains in broth or in the condensation fluid in agar tubes. In broth at 35–37° C. it forms a uniform slight turbidity after two to three days; then flakes appear which at the bottom of the tube form a more or less coherent viscid whitish precipitate. In this stage cover-glass specimens show long curved chains of the character shown in fig. 27.

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[1] Rosenbach: *Mikroorganismen bei den Wund-Infectionskrankheiten des Menschen*, Wiesbaden, 1884.

When recent cultures are inoculated into the subcutaneous tissue of rabbits, a distinct blush and slight swelling is noticed after twenty-four hours, after forty-eight hours, or at latest after three days, the blush has passed away ; in some instances the swelling at the seat of inoculation increases, and a minute abscess is noticed now or during the next following days. In guinea-pigs a thickening and inflammation are noticeable at and about the seat of inoculation after a day or two, which increases during the next few days, but in most cases has passed away by the end of the week; in very few instances a purulent abscess is found after four or five days. In white mice, in only a small percentage of cases is an abscess formed ; but if large quantities are injected, necrosis of the subcutaneous tissue occurs, and in some instances acute fatal septicæmia, i.e. death after thirty-six to forty-eight hours. In these cases the spleen is found enlarged and all the viscera greatly congested ; in the blood and the spleen the streptococci can be demonstrated by cover-glass specimens and by culture. In the rabbit intravascular injection of even large quantities produces no result, unless the animal has been previously made ill by the injection of toxic substances ; under these conditions a general infection with the streptococci is produced, and the animal dies in two to five days ; ulcerative endocarditis is noticed, if previous to the injection injury to the aortic valves has been produced (Wyssokowitsch).

It is maintained by many observers that the streptococcus pyogenes, such as occurs in acute, sub-acute, and chronic phlegmon, is always the same species, and is identical with the one isolated by Fehleisen in erysipelas. The writer is confident that the name streptococcus pyogenes does not cover only one species, but is the name of a group of different species, varying in many details, though they all have a number of characters in common ; only on closer observation in the different media and by the result of inoculation of animals can these differences be made out. The streptococcus pyogenes obtained from acute phlegmon is most decidedly not the same as the streptococcus pyogenes which is obtained from chronic necrosis ; it is not the same as that obtained by Fehleisen from erysipelas ; nor is it the same as that obtained by the writer from scarlatina, although they may and do occur together ; e.g. in erysipelas, both the streptococcus pyogenes and the streptococcus erysipelas were found together by Fehleisen, the former in the older or central, the latter in the younger or peripheral part of the erysipelatous patch. In scarlatinal cervical glands the writer found the streptococcus pyogenes together with the streptococcus scarlatinæ ; so also in the ulceration of the teat in the Hendon cow disease, in the superficial part of the ulcer the former, in the depth of the inflamed skin and subcutaneous tissue the latter, was found. In the secondary inflammatory foci following scarlatina and diphtheria, the streptococcus pyogenes has been isolated by Löffler and others, and also in the cutaneous eruption of infantile hereditary syphilis.

To say that, because the streptococcus pyogenes of acute and chronic phlegmon is in its cultural characters extremely similar to the streptococcus erysipelatos, both are identical, would be illogical and contrary to clinical observation. An acute simple phlegmon or ulcer, acute or chronic, is not erysipelas, this latter being as well defined an acute infectious disease as, say, anthrax is, both as to its pathology and symptoms. Streptococcus pyogenes is found in the tissue of many ulcerations, yet no erysipelas follows ; streptococcus pyogenes is obtained occasionally from pustules, yet in these cases there is no sign of any erysipelas. Streptococcus pyogenes obtained from acute or chronic abscess and inoculated as recent cultures into the rabbit's ear does not produce that distinct erysipelas that Fehleisen's true streptococcus erysipelatos does. Some observers find no difference in the result of inoculation into the rabbit's ear between the streptococcus pyogenes of acute phlegmon and the streptococcus isolated from erysipelas; but this might be due to the fact that they had not got hold of the streptococcus erysipelatos, although taken from erysipelas, or that they used an attenuated culture. It is, however, right to mention that the streptococcus erysipelatos by continued sub-culture loses gradually the power of producing erysipelas.

The streptococcus pyogenes as obtained from acute or chronic phlegmon is not identical with the streptococcus shown by Koch to cause progressive necrosis in mice, although both are extremely alike. The streptococcus pyogenes is not identical with some species of streptococcus which can be obtained from the fluid of the mouth, from soil, and from ulcers. There are streptococci which though similar to the streptococcus pyogenes are yet not identical, e.g. a streptococcus obtained from ulcers on the teats of cows (Wiltshire disease), which does not grow at temperatures above 25° C.; a streptococcus from the fluid of the mouth, which does not grow below 25° C.; Schütz described a streptococcus connected with, and causing infectious pharynx-abscess in the horse (Druse), which does not grow below 25° C.; Löffler obtained a streptococcus articulorum from diphtheria; Flügge described a streptococcus malignus which causes acute septicæmia in mice; Nicolaier described a streptococcus septicus which he found in soil. All these streptococci are similar, and only on careful cultural and experimental observation can they be distinguished from one another, though some of them with difficulty, even under these conditions.

(6) *Micrococcus tetragonus* is occasionally found in pus. Gaffky first described it in the purulent sputum of pulmonary tuberculosis, but it has been of late years also found in other localities, notably, purulent inflammations connected with tubercle. The chief character of the coccus is its arrangement in fours. It grows fairly rapidly in gelatine, forming round yellow colonies, on the surface of the gelatine white prominent droplets. This microbe acts virulently on mice and guineapigs, particularly on the former, which on subcutaneous inoculation with small doses succumb in the course of three or four days from septicæmia, the blood-vessels of all viscera containing the microbes.

(7) *Bacillus pyocyaneus* is the microbe found in blue-green pus—in fact, it is the organism which produces the blue-green colour. Gessard and Charrin (Gessard: Thèse de Paris, 1882. Charrin: Communication à la Société anatomique, December 1884) first described the microbe. Gessard particularly isolated the blue pigment produced by it, pyocyanin. When isolated by gelatine plates from blue-green pus the microbe grows as translucent colonies irregular in outline and showing a fine radial striation, the gelatine gradually assuming a greenish colour. The gelatine is liquefied and of a uniformly greenish colour; on agar it forms a white film, while the agar becomes tinted greenish; on potato it forms a brownish film, while the substance of the potato underneath assumes a greenish colour. It has pathogenic action on guineapigs.[1] Under the microscope it is an extremely minute and thin cylindrical rod (*see* fig. 28).

(8) *Bacillus pyogenes fœtidus* of Passet is the bacillus which is found in malodorous pus. This microbe is a short rod, generally arranged as dumb-bells: it shows sluggish motility, and is about 1·45 μ long and 0·58 μ thick.

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[1] When a few divisions up to half a Pravaz syringe of the broth culture be injected subcutaneously, the animals become ill and die in from two to four days, showing peritonitis, pericarditis, and pleuritis, with copious membranous and purulent exudation, which contains abundantly the bacilli.

In gelatine plates it forms round white colonies, thicker in the centre than in the periphery. On potato it grows as a brown thick film. Small doses inoculated in animals produce no effect, larger doses sometimes abscess. (Passet.)

Karlinski gives as the result of a large number of observations on purulent matter of man the following list ('Centralbl. f. Bact. und Parasit.,' VII., No. 4, p. 115):—

Disease	Staphylococcus pyogenes aureus	Staphylococcus pyogenes citreus	Staphylococcus pyogenes albus	Streptococcus pyogenes	Micrococcus tetragonus	Bacillus pyogenes fœtidus	Bacillus of Friedländer	Bacillus anthracis
Mastitis, 36 cases . .	22	4	4	6	—	—	—	—
Subcutaneous abscess, 30 cases	10	2	8	6	2	2	—	—
Phlegmon, 24 cases . .	—	—	—	24	—	—	—	—
Furuncle, 20 cases . .	9	—	10	—	1	—	—	—
Bubo, 17 cases . . .	8	1	1	7	—	—	—	—
Subperiosteal abscess, 16 cases	6	—	10	—	—	—	—	—
Panaritium cutaneum, 16 cases	7	—	9	—	—	—	—	—
Abscess of gums, 10 cases .	1	—	4	1	3	1	—	—
Hordeolum, 10 cases . .	6	—	4	—	—	—	—	—
Otitis media, 4 cases . .	2	—	—	—	—	—	2	—
Carbuncle, 4 cases . .	2	—	1	1	—	—	—	4
Osteomyelitis, 3 cases . .	2	—	1	—	—	—	—	—
Summary . . 190	75	7	52	45	6	3	2	4

The three species, staphylococcus pyogenes aureus, staphylococcus pyogenes albus, and the streptococcus pyogenes, from their distribution deserve then the most close consideration, and the question that at once presents itself is this, Are these microbes the cause of the disease? There can be little doubt from what we have seen above, that experimentally the three species can produce primarily inflammation, and there can be also no doubt that, in a variety of secondary inflammations in man, following sometimes other infectious disorders, as scarlatina, diphtheria, variola, typhoid fever, measles, one or the other species of these microbes is found in the foci of those secondary inflammations. Now, it may be admitted that their presence in these secondary foci might not be the primary cause of the foci, but only the result, for it is quite possible to imagine that, from one cause or another, a loss of vitality of a particular tissue having been established, these microbes derived from a diseased surface can pass into such a disorganised tissue, and can here multiply (*see* above, Wyssokowitsch's experiments). That the actual inflammation and suppuration in these secondary foci are due to these microbes, is shown by the fact, that experimentally they can produce suppuration. That also in the primary inflammation and suppuration these microbes play an essential *rôle*, i.e. are really the cause of the inflammation and suppuration, is extremely probable. It is a notorious fact that in many traumatic lesions of the skin no suppuration follows, while in others neither more nor less extensive, suppuration sets in. Thus, for instance, splinters of wood, glass, wire, &c., inserted under the skin are sometimes followed by a slight reaction, which passes off in a day or two, and is not followed by any suppuration, but on other occasions cause marked inflammation and suppuration.

A traumatic injury even of considerable extent produced under aseptic conditions and treated aseptically, as is the case in Lister's and similar methods, as a rule heals by first intention, and does not lead to suppuration, whereas under other conditions suppuration follows as a rule. A blow by which the surface of the skin is not broken does not, as a rule, lead to suppuration, though in some few instances it is followed by suppuration. These facts seem easily explained on the assumption that in one set of cases the pyogenic staphylococci and streptococci do not happen to enter into the wound, e.g. in some cases of splinters, or are kept out of the wound, e.g. in aseptic treatment, and therefore no phlegmon and no suppuration follow, while in the other set of cases one or the other species finds entrance, and then by its multiplication causes suppuration. From this it must not, however, be concluded that every kind of phlegmon and suppuration is caused by the pyogenic microbes; for it is well known that such is not the case; a burn, or an injection under the skin of chemical irritants (e.g. oleum crotonis, turpentine, alcohol, ammonia, tincture of iodine, tuberculin, &c.) produces phlegmon and suppuration. Besides, various kinds of infectious phlegmons and suppurations are caused by other than pyogenic micrococci, as will be evident by-and-by (e.g. tubercle, glanders, actinomycosis).

A further consideration in connection with the pyogenic micrococci is this: like some saprophytic microbes, the pyogenic micrococci also—at any rate in some instances—produce noxious chemical substances; if large quantities of these are produced at the primary seat of inflammation, and are absorbed into the system, a condition similar to sapræmia is set up, manifesting itself by rigors, and fever temperature with or without intestinal disturbances; and it is precisely under such conditions of depressed vitality that an invasion of the whole body by the microbes, from the primary seat of inflammation and suppuration, may occur. As a result of such an invasion, secondary foci of inflammation follow in the lymph glands, internal viscera, bones and joints, with the formation of metastatic abscesses. Such secondary foci of suppuration running a sub-acute or chronic course represent *pyæmia*, or if the invasion is copious and universal an acute *septicæmia* is the result. In the latter case a general congestion of the viscera, and swelling of the spleen, will be found, and on microscopic examination of sections of the lungs, liver, kidneys, and the lymphatic glands, signs of diffuse or localised foci of inflammation—sometimes more, sometimes less abundant—will be apparent. It seems feasible to assume that in those cases in which no pyæmia and no septicæmia follow a primary inflammation and suppuration, no secondary successful invasion by pyogenic microbes has taken place; and, further, that if a secondary invasion does occur, it is due to the absorption of noxious chemical substances and a general depression of the vitality of the blood and tissues. It cannot be assumed that no absorption of the pyogenic microbes occurs, for there is nothing that would prevent those microbes from finding their way from any primary focus of inflammation or suppuration into the lymphatics and into the blood-vessels; but though this must be assumed to occur under all conditions, their settling down and multiplying does not take place under all conditions, since as a matter of fact not all primary inflammations, be they traumatic or be they associated with specific infectious diseases, are followed by pyæmia or septicæmia; on the contrary, it is rather the exception that such is the case. The reason for this absence of secondary foci of inflammation and abscess (pyæmia) or of a general and acute flooding of the system with the living pyogenic microbes must be sought in the normal power of the blood and tissues to destroy those microbes; but if this power be inhibited or exhausted, e.g. by the absorption of chemical septic substances and injury to the vitality of the tissues, or if the number of the microbes absorbed be too large, then a secondary infection will be the result.

Pyæmia, i.e. disseminated phlegmons, and suppurations in distant localities (lymph glands, internal viscera, bones and joints), is therefore to be regarded as due to a secondary infection, i.e. an invasion by the pyogenic microbes, settling down and multiplying in various distant localities, and there causing inflammation and suppuration ; and it is a sub-acute or chronic process as compared with certain forms of *septicæmia* caused by a copious and general flooding of the system with the pyogenic micrococci. This must be further distinguished from the septic intoxication caused by the absorption of septic chemical substances in sufficient quantities, produced at the seat of the primary inflammation, which in itself may be, and in all probability is, that which initiates and facilitates those *secondary infections*.

In caries of the teeth, various species of micrococci, bacilli, and vibrios occur ; the former two have been found to form continuous masses filling the dental tubules of the affected parts and the neighbourhood, but whether they are the primary cause of the disease remains yet to be proved experimentally.

Miller has given in 'Mikroorganismen der Mundhöhle,' Leipzig, 1889, numerous careful observations on the microbes of the diseased teeth and jaw ; also David in 'Les Microbes de la Bouche,' Paris, 1890.

Various necrotic processes in the viscera—necrotic foci in the kidneys, liver, cornea, and other organs—have been observed in man and animals (*see* Baumgarten, 'Lehrbuch der patholog. Mycologie,' I.) in which the necrotic foci were clearly due to the presence of streptococci ; but all these must not be considered as belonging to a single species of the streptococcus pyogenes, as is done by Baumgarten and others.

A progressive necrosis, leading to death in a few days, has been observed in mice by Koch, the tissue being invaded, and the necrosis caused by a streptococcus.

In the Aleppo bubo, Riehl found numerous cocci in the round cells constituting the tumour, but they have not been cultivated.

Ulcerative Endocarditis

In the experiments by Wyssokowitsch with streptococcus pyogenes, mentioned above, the cultures were injected into the vascular system of rabbits whose aortic valves had been previously injured ; the result was ulcerative endocarditis with copious multiplication of the microbe on the endocardium. In human ulcerative endocarditis, the blood-vessels of the heart muscle near the ulcerated endocardium are found plugged with crowds of micrococci ; so also the tissue of the endocardium contains numerous continuous smaller or larger masses of cocci, and the ulcerated surface is almost covered with a continuous layer of them ; the characteristic papilliform filamentous and fringe-like projections from the endocardium in the verrucous form of endocarditis are themselves sometimes covered with them, and contain numerous cocci in their tissue. Experiments by plate or tube cultivation yield pure cultures of these cocci ; in some cases they belong to the species above described as staphylococcus aureus liquescens ; in others they are the species described as staphylococcus albus ; and in others again they belong to the species of streptococcus, probably streptococcus pyogenes.

Weichselbaum, Wyssokowitsch, Ziegler, Bonone, Hare, and Prudden found in some cases of ulcerative endocarditis the staphylococcus pyogenes aureus, but in others the staphylococcus albus or streptococcus pyogenes.

Netter found the bacillus pneumoniæ of Friedländer; and Weichselbaum describes cases of ulcerative endocarditis, some of which were associated with the diplococcus pneumoniæ, others with the streptococcus pyogenes, and others again with both. F. W. Andrewes made numerous observations and experiments on staphylococcus pyogenes aureus, in connection with ulcerative endocarditis. He found that the staphylococcus aureus taken from acute abscess (mastitis) when injected into the vascular system of rabbits is capable of producing foci of inflammation in the kidney, in the interior of the aorta, and in the myocardium of the ventricles of the heart. In some cases of human ulcerative endocarditis he found the staphylococcus aureus, in others the streptococcus pyogenes.

ERYSIPELAS

In erysipelas, the skin in its whole thickness is the seat of inflammation. In this process the skin appears swollen and red, the redness is more or less sharply outlined, serrated, and it and the swelling gradually spread into larger areas, but as the redness and swelling spread in the periphery, in the middle parts the skin becomes again livid. In microscopic sections the skin is immensely congested in the red parts, the blood-vessels greatly distended and filled with blood, the connective tissue is œdematous and contains leucocytes; these are chiefly present in the superficial layer of the corium, and from here extend into the stratum Malpighii; in the livid parts the number of leucocytes is greatly increased, and they pervade all parts of the corium more or less uniformly. In the peripheral red portions, the lymphatics are greatly distended and plugged by micrococci (Lukkomsky), and it is this condition which induces the congestion of the vessels and the exudation of the lymph and leucocytes. As the multiplication of the micrococci increases and spreads, the nearest lymphatics become filled and plugged with them, and this again causes congestion of the blood-vessels of this part, and exudation of lymph and leucocytes, and in this way the redness and swelling follow the multiplication of the micrococci in the lymphatics. In the parts first affected the congestion passes off first, but the lymphatics remain plugged with the cocci, and then many of them are also found outside, i.e. in the connective tissue of the skin (Ziegler); at the same time the number of leucocytes here greatly increases, and they are found to form a diffuse infiltration of the subcutaneous tissue, the corium, the papillary layer and of the stratum Malpighii. In the variety of erysipelas known as erysipelas bullosum, small cavities appear in the superficial layer of the stratum Malpighii; these cavities as in other inflammations of the skin (e.g. foot-and-mouth disease, vaccinia, variola) are due to the accumulation of lymph in the interstices (cement or interstitial substance) of the epithelium; a few leucocytes also find their way into these cavities. As the lymph increases in these cavities the epithelial cells surrounding them become degenerated and break down; the inter-epithelial spaces and lacunæ are smallest in the red part, they increase towards the oldest or livid part, and here they attain such size that they become more or less confluent, separated only by thinner filamentous septa, the remains of compressed streaks and trabeculæ of epithelial cells; all these cavities contain cocci, clear lymph, *débris* of epithelial cells, and leucocytes; the central or largest bullæ extend from the stratum corneum down to the corium, and when the former breaks, the highly infiltrated corium becomes exposed.

Fehleisen has shown[1] that the cocci in the lymphatics of the red marginal part, as also from the deep parts of the skin in the central portions, are the *streptococci of erysipelas*, but that besides these, streptococcus pyogenes can also be obtained from the superficial layers of the central parts and from those of the peripheral parts. The streptococcus erysipelatos can be easily cultivated from the fluid of the marginal red part in the genuine erysipelas, such as occurs sometimes as a special acute febrile disorder, involving the face, neck, and scalp. The writer has had two such cases where genuine erysipelas with high fever occurred in adults; it commenced in the face and spread from here over the upper part of the neck, on the forehead and all over the scalp; the temperature was 102·5° on the evening of the third day, and the erysipelas was of the bullous kind, viz. as the redness passed into the periphery the older livid part became bullous, then the surface dried up into brown scales, which gradually broke and desquamated. From the marginal red part, after well cleaning it with perchloride of mercury solution, by a prick, lymph was received into a capillary glass pipette, and with this plate cultivations were made. Numerous colonies came up, which all proved to be the streptococcus erysipelatos.

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[1] Fehleisen, *Die Aetiologie des Erysipels*, Berlin, 1883.

With the cultures of the true streptococcus erysipelatos, Fehleisen has produced distinct erysipelas by inoculation into the skin of the ear of rabbits; after twenty-four hours the skin of the ear shows a deep blush around the place of inoculation, and is slightly swollen; this blush and swelling increase and spread during five or six days over the whole of the ear, on to the scalp and into the neck; the bullous and scaly change is also very marked. The writer has repeated these experiments, and can fully confirm them, as also the other fact stated by Fehleisen, viz. that from the spreading and swollen part of the skin of the ear there is no difficulty in obtaining pure cultures of the streptococcus erysipelatos. The cultures and microscopic specimens of this streptococcus are difficult to distinguish from the streptococcus pyogenes, but inoculation into the rabbit's ear shows this difference. Injection of large quantities into the vein produces in the rabbit in a large percentage of cases acute septicæmia, fatal in thirty to forty-eight hours; the spleen is enlarged, all viscera are congested, and from the spleen, lung, liver, and from the blood of the general circulation the streptococcus of erysipelas can be easily recovered by cultivation.

When the streptococcus erysipelatos is carried through several generations on gelatine, its virulence suffers a distinct diminution, since the effect on the rabbit's ear becomes greatly diminished. From a twelfth sub-culture, inoculation into the rabbit's ear produces after twenty-four hours a distinct blush; this spreads a little during the next day or two, and the skin is tumid, but after this the redness and swelling again subside.

Whether or not the streptococcus isolated from human erysipelas by Passet, Bonone and others, and assumed to be the streptococcus pyogenes, was the real streptococcus erysipelatos, but representing merely an attenuated form, is a matter of conjecture; the facts brought forward by Fehleisen and others, viz. that two species of streptococci can be originally obtained by culture from the erysipelatous skin, and their differences proved by inoculation into the rabbit's ear, seem definitely to contradict the above conjecture. The above observers, in fact, maintain that the streptococcus pyogenes of abscess and ordinary phlegmon is identical with the streptococcus of Fehleisen, that is, of erysipelas, the latter representing merely an attenuated form of the former. E. Fränkel ('Centralbl. f. Bact. und Parasit.,' VI., p. 691) is quite sure of the identity of the two microbes; but notwithstanding this, on pathological and clinical grounds, a doubt of this alleged identity may yet be permitted.

An important series of experiments made by Fehleisen was this, that he produced with cultures of the streptococcus erysipelatos distinct and typical erysipelas in the human subject; these experiments were made in order to cause sarcomatous tumours to disappear, in conformity with older surgical experiences; and in this he succeeded in several instances, in which he produced by his cultures true erysipelas of the skin in the part containing a tumour; the erysipelas passed off, and the tumour also disappeared, and became absorbed.

This question of the alleged identity maintained by some observers of the streptococcus pyogenes and streptococcus of erysipelas illustrates better than any other case, on the one hand, the difficulty existing in distinguishing two similar microbes, and on the other the want of appreciation of pathological and clinical facts in drawing conclusions from bacteriological investigations alone. No clinical observer will admit that erysipelas is an ordinary phlegmon, though all bacteriologists may not be able to distinguish the one species from the other. Of course the suggestion is not wanting that owing to an increase in virulence, due to some unknown cause, the streptococcus pyogenes, growing in and causing ordinary simple phlegmon, may become the streptococcus of erysipelas and cause erysipelas, while in a similar manner this latter organism by attenuation, due to some cause or other, may become attenuated and may degenerate thereby into the streptococcus pyogenes. While such an assumption is based on very insufficient evidence, the other alternative, viz. that the two are physiologically different species, though they may not be easily distinguished from one another, is based on the fact that the two species have an altogether different distribution, the one, streptococcus pyogenes, in pus of acute and chronic abscess and in common phlegmon, the other in erysipelas—a type of a specific disease as distinct as any, both pathologically and clinically. It is just as difficult to imagine that an ordinary non-infectious sore throat accompanying an ordinary cold is an attenuated form of diphtheria as that an ordinary phlegmon is an attenuated form of erysipelas; no clinically experienced observer would consider a sore throat associated with an ordinary cold as diphtheritic sore throat, any more than he would admit a common phlegmon, or common abscess, to be erysipelas. Such an assumption of the identity of causes in maladies so utterly different as common phlegmon and erysipelas seems opposed to the known fundamental facts of the specific diseases.

CHAPTER XIII

SEPTICÆMIA

WE have on previous pages pointed out that a distinction must be drawn between septic *intoxication*, sepsis, or sapræmia, on the one hand, and septic *infection*, or septicæmia, on the other. Under septicæmia is understood an acute febrile disturbance, due to the presence and multiplication of microbes within the blood,[1] generally ending fatally, between twenty hours (or even less) and two or three days, rarely later. All vessels contain the microbes, the organs of the chest and abdomen are congested,[2] extravasation of blood occurs in the serous membranes, also in the lung, spleen, and intestines; the spleen as a rule is enlarged, its vessels are engorged; the intestinal mucous membrane is in a state of congestion and inflammation. In many small vessels, e.g. in the liver, kidney, spleen, and lung, the number of the specific microbes has so largely increased that veritable thrombi are formed by them; in such places the tissue around the vessels is found in a state of necrosis—coagulation necrosis. This condition is often found in the liver, when the central vein of a lobule and a number of capillaries leading into it are distended and plugged with solid masses of the microbes; the liver cells of such a part are large and opaque; they do not stain in dyes, their nucleus is swollen and clear—such parts correspond to necrotic tissue; in the kidney many of the capillaries of the glomeruli are also plugged with masses of the microbes, also some of the fine vessels in the cortex between the convoluted tubes and in the medulla between the straight tubes; the rest of the glomerulus is swollen and degenerated; in the convoluted tubes and in the straight tubes of the cortex, the epithelial lining of the tubes is swollen, dark, granular, and in a state of disintegration; in the lungs many lobules show great congestion of the capillaries surrounding the alveoli; in these the epithelial cells are desquamating, and blood is occasionally found extravasated into their cavity; pericardial, pleural, and peritoneal exudations occur: the latter is very common.

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[1] The first systematic experimental work on the relation of micro-organisms to septicæmia was published by Koch in *Die Aetiologie der Wund-Infectionskrankheiten*, Leipzig, 1878.

[2] The pathology of sapræmia is very much the same as that of septicæmia, since both are probably the result of the action of similar kinds of toxic chemical substances, in the former produced at a given primary focus, in the latter produced in the circulating blood by the microbes distributed in the body.

The specific microbes can be easily demonstrated by cover-glass specimens; and by culture from the heart's blood, and from all congested viscera, particularly the spleen, though there obtain great differences in these respects, since in some the number of microbes in the blood of the general circulation is very limited, while in others it is abundant. From the spleen they can always be recovered in considerable numbers.

We have on a former page pointed out that where, in any locality, extensive inflammation, ulceration, or suppuration is going on, the absorption of chemical poisonous substances, elaborated by microbes at those localities in sufficient quantities, produces sapræmia, which may then induce, or rather pave the way for, a secondary invasion of the microbes from that primary focus, whereby a true infection is produced, which may, and in some cases does, cause septicæmia, the microbes multiplying in the blood abundantly. But a sapræmia may occur without subsequent secondary infection, and the sapræmia may be in some cases so extensive, owing to the large amount of matter absorbed, that it causes death; the pathological symptoms are the same as those of the septicæmia, as naturally they would be, but there are none of the microbes of the primary focus to be found in the blood, spleen, or other viscera. We said just now that the pathological appearances would be naturally the same as in the septicæmic infection: sapræmia being caused by the absorption of toxic chemical substances produced by the microbes at the primary focus, while septicæmia following such a primary disease is due in the first instance to a general invasion of the blood and tissues by the microbes and subsequently to the action of toxic substances produced by the microbes in the blood and tissues.

While giving these general outlines of what is usually considered as septicæmia, we cannot shut our eyes to the fact that the term septicæmia is applied to a group of diseases in no marked manner or degree well defined from other diseases not strictly coming under this head. At present various diseases of the true type of infectious and contagious diseases fall under this group, e.g. fowl cholera, malignant anthrax, swine erysipelas, swine fever, and human erysipelas. Now all these diseases are as true and typical infectious diseases as small-pox or scarlet fever. There is nothing fundamental by which septicæmic diseases, anthrax, small-pox, or scarlet fever can be said to be separated from one another. True in the septicæmic diseases, e.g. surgical septicæmia, *post-mortem* wounds septicæmia, various septicæmic diseases in rodents and other animals, infection starts, as a rule, from a wound, i.e. by inoculation; but there are others in which infection is most certainly produced naturally by way of the respiratory and alimentary canal, e.g. in genuine erysipelas of the face, where in the affected individual infection by inoculation is out of the question, or in anthrax of sheep and cattle, where infection is carried out naturally by the alimentary or respiratory tract, or in the form of anthrax in the human subject known as woolsorters' disease, or in intestinal anthrax; again in a septicæmic disease to be described as ragsorters' disease, infection is also effected by the respiratory tract. In fowl cholera, in swine erysipelas, and in swine fever, infection under natural conditions is carried out by the alimentary and respiratory tract; and in these respects there is therefore no difference to be drawn between these diseases and, say, the acute exanthemata. Nor can we establish a difference between them and the acute exanthemata on account of the latter showing some well-marked cutaneous eruption, for in swine erysipelas, in human erysipelas, in malignant pustule, there are just as characteristic cutaneous lesions present. Further, we cannot say that as regards the distribution of the microbes there is a fundamental difference. True, in many septicæmic diseases the microbes are universally present in the blood, but there are marked differences in this respect between the different forms; for while in some the microbes in the blood are very numerous, e.g. anthrax, and certain forms of septicæmia to be mentioned presently (Davaine's and Koch's septicæmia, fowl cholera), they are scarce in the blood in others, e.g. malignant œdema, swine fever, and swine erysipelas: they are not easily found in the blood in human erysipelas. Nor do we find any fundamental difference as regards progress and duration. True, many septicæmic diseases are rapid (duration from sixteen to twenty hours, to two or three days), but there are some belonging to this class which pursue a longer course, e.g. swine fever. We must therefore consider that the term septicæmia is an artificial one, and that the group of diseases indicated by it is not fundamentally different from other acute infectious diseases not generally included in this group. When septicæmic infection occurs after direct inoculation—as in accidental, surgical, puerperal, *post-mortem* infection, or after experimental inoculation of cultures of the septicæmic microbes into animals—the multiplication of the microbes within the blood produces those toxic substances which, when in sufficient quantity, set up the symptoms of the disease and ultimately cause death.

We will now proceed to describe the various specific microbes which have been proved to cause septicæmia in man or in animals, omitting those which have been already mentioned as capable of producing under certain conditions septicæmic infection in rodents, e.g. the pyogenic staphylococci and streptococci, as also certain microbes occurring in saliva (Pasteur and Sternberg) and in normal human fæcal matter (Bienstock, Brieger), the typhoid fever bacillus, and the micrococcus tetragonus (on mice and guineapigs) occurring in purulent human tubercular sputum, and the cholera spirilla of Koch and those of Finkler (on guineapigs).

A. *Davaine Septicæmia in Rabbits.*—This is a septicæmia which Davaine first produced by injecting putrid ox's blood into rabbits. It is now known that a small bacillus (formerly considered as bacterium) is the microbe, which by its great multiplication and universal distribution in the circulating blood causes the disease and death. The microbe is present in the blood in great numbers, nearly as great as those of the blood-corpuscles; in stained specimens the rods, which are short and oval, show a stained granule at each end with a clear space in the middle; the length of the rods is about 1·5 μ, the thickness about half of the length. The rods are non-mobile, and from the heart's blood, and all other tissues, pure cultures can easily be made. In plate cultures, after about two days, minute white dots are visible; under the microscope they appear as flat circular discs, white in reflected, yellow brown in transmitted light. After several days the colonies are larger, and appear thicker and broader in the centre than at the periphery, which appears more or less concentric owing to regular differences in thickness. At maximum growth the colony does not exceed one to two millimetres. In stab culture the stab is occupied by a whitish line; under the microscope this is seen to be made up of minute droplets and dots, whitish in reflected, yellow brown in transmitted light. In streak cultures the streak is represented by a narrow whitish band of irregular outline, thicker in the middle than at the margin. After two to three months the cultures in gelatine are dead.

Rabbits, mice, fowls, pigeons, and sparrows are very susceptible (Koch) to the inoculation of minute doses of the culture or of the blood of an animal previously dead of the disease; guineapigs and rats are insusceptible (Koch). When rabbits are inoculated with a trace of the blood of a rabbit dead of the disease, or with a trace of the culture, after ten to twenty-one hours they show a distinct rise of temperature; in some cases the animals show spasms and a fall of temperature before the end of the first sixteen hours, and are dead before the day is over; but in some cases, particularly after inoculation with minute traces of culture, death does not take place in less than thirty-six to forty-eight hours. The bacilli are found very numerously in the blood-vessels of all organs. The spleen, liver, lymph glands, and lungs are highly congested, as also the intestines; extravasations are rarely found, and then only in the omentum and lungs; peritonitis is noticed only in a small percentage of cases, and then only when the omentum shows the extravasations; the serous covering of the intestines is greatly injected. As a rule, these symptoms are more pronounced if death does not occur before the second day.

This septicæmia has been minutely studied by Koch, who investigated the susceptibility of various animals towards these bacilli.

B. *Septicæmia in Rabbits* (Koch).—Oval cocci 0·8 μ to 1·0 μ in length, about 0·6 μ. in breadth. Putrid meat-infusion injected by Koch into rabbits produced death by septicæmia; the spleen was found much enlarged and all internal viscera congested. The cocci are numerously present, generally isolated, occasionally in clumps, in the capillaries of all viscera. The cultural characters of this organism have not been studied by Koch. The writer has produced a septicæmia in rabbits by subcutaneously inoculating them with sputum of human croupous pneumonia, which septicæmia bears a great resemblance to the above; the symptoms were the same, the cocci were the same, and their distribution in the organs, particularly in the kidneys, appeared the same as described by Koch. From the blood of the rabbits dead from the disease, cultures were easily obtained; the colonies were whitish, round, and convex; at the end of a week they grew to 4–5 mm. in breadth, and in transmitted light appeared brownish; in streak cultures they formed a whitish, irregularly outlined, moist-looking band, which appeared either of uniform thickness or a little thicker at the margin. Stab cultures several days old appeared in transmitted light to be made up of brownish droplets; during the first few days the stab when viewed with the unaided eye appeared as a whitish line. Mice and rabbits were found susceptible to the cultures, but comparatively large doses ($\frac{1}{4}$–$\frac{1}{2}$ c.c. of broth-culture) had to be injected.

C. *Malignant Œdema* (Koch.)—This disease has been produced by Koch in guineapigs by the subcutaneous injection of recently manured garden earth. An extensive œdema occurs at and about the seat of inoculation; the œdema is accompanied by hæmorrhage into the subcutaneous tissue, and is of an offensive odour; it spreads during the second day, leads to gangrene of the subcutaneous and muscular tissues with the formation of gas bubbles, and the animals die in from twenty-four to forty-eight hours: the spleen is found congested, so also are the liver, kidney, lungs, and intestines. In the œdematous exudation and in the spleen long mobile bacilli are present, either singly or in filaments and long chains; their number in the blood is comparatively small; the size of the short bacilli is 2–3·5 μ in length, and 1 μ in thickness; their ends are more or less rounded. Many bacilli are in the form of chains and filaments. The œdematous fluid, and the blood, inoculated into fresh guineapigs produce the fatal disease.

Rabbits are also very susceptible to the disease; and at the seat of inoculation œdema is produced. Mice are very susceptible, and die before the end of the first day, but no œdema is present at the seat of inoculation. All the viscera are congested, and the spleen is enlarged; the blood of the spleen, the exudation of the peritoneum, and the pleura, contain the bacilli. A sure diagnosis, and differentiation from anthrax bacilli, to which the œdema bacilli bear a certain likeness, can with certainty be made by cultures.

The cultural characters of this bacillus show that it is altogether different from that of bacillus anthracis; although in size and general aspect in the fresh state, and in stained cover-glass specimens, it is not unlike bacillus anthracis, yet it is quite different in its action on animals, in the condition of the spleen of the inoculated animals, and in its small numbers in the blood of these. When cultivated it shows the following characters: The œdema bacillus is *anaërobic*, since it does not show growth on the surface of nutritive media; it grows only when planted in the depth; in gelatine (in the depth) it forms characteristic globular colonies of different sizes, opaque and liquefied, their margin more opaque than the centre and finely striated. The growth and liquefaction proceed gradually and slowly, till all the gelatine is liquefied; at the bottom of this is a voluminous greyish white filamentous mass. It grows best in gelatine to which 1–2 per cent. of grape sugar has been added. In solid agar agar it grows well, producing uniform turbidity all through the medium, with floccular condensations and numerous gas bubbles. Solidified blood serum is liquefied by the bacillus. The cultures act virulently, provided comparatively large quantities are injected.

Oval bright spores are formed very rapidly in the short bacilli, either in the middle or at one end; the spores are thicker than the bacilli themselves; and the bacilli in the œdematous fluid contain spores. The œdema bacillus is of great importance, since by the observations and experiments of Chauveau and Cornevin, Brieger, and others, it has been shown that surgical gangrene (progressive gangrenous emphysema) in the human subject is caused by the same bacillus. It seems that many a soil containing putrid animal substances, such as hay dust, rag dust, offensively smelling filth of dust bins, offensively smelling exudations, gangrenous discharges, &c., contain the œdema bacillus and its spores. Horses, pigs, and sheep are susceptible to this malignant œdema, provided large doses are inoculated; cattle are not susceptible. As mentioned above, guineapigs are the best experimental animals, since inoculation produces a typical, emphysematous, spreading œdema, with fatal result.

Pasteur has studied this septicæmia in guineapigs; hence it is also called Pasteur's septicæmia. The bacillus was called by him vibrio septique. Roux and Chamberland have demonstrated, in the broth cultures of this microbe, toxic substances, which, separated from the bacilli and injected into animals, cause a transitory illness proportionate to the amount injected, and thereby confer immunity against the injection of the virulent bacilli themselves. But this immunity does not last long, and is not produced if the quantities used are too small.

With recently manured garden earth, the writer has produced in guineapigs, rabbits, and mice a disease which, in its symptoms, is in many respects similar to the malignant œdema of Koch. But the microbe is totally distinct; it is a short, mobile rod, the long cylindrical and filamentous forms being few. It is distinctly *aërobic,* forms also gas bubbles in the depth of the gelatine, but grows well in ordinary nutrient gelatine; does not liquefy the gelatine, and does not form spores. The œdema fluid at the seat of inoculation is crowded with the bacilli, the blood and spleen containing only comparatively few bacilli (fig. 41).

Flügge has isolated a pseudo-malignant œdema bacillus from recently manured garden earth, which resembles Koch's malignant œdema bacillus, but is non-pathogenic.

D. *Mouse Septicæmia of Koch.*—By inoculation of filthy water into mice, Koch produced an acute and fatal septicæmia, which, owing to the peculiarity of the microbe, is of great interest. At the seat of the inoculation there is found slight hæmorrhage, the internal viscera are greatly congested, and the spleen is not much enlarged; the animals die during the second day. In the blood of all parts are found in very large numbers exceedingly minute bacilli, some longer than others; but all are very fine, and many of the white blood-corpuscles are quite filled with them, and at the same time swollen up. In the lungs there is slight hæmorrhage into the alveolar tissue; everywhere one sees the swollen leucocytes completely filled with the minute bacilli. Some of these become free owing to the disintegration of the leucocytes. Sections through the lung, stained carefully in fuchsin and then in methyl blue, show the nuclei of the tissue and of the leucocytes blue, the bacilli bright red.

Cultivations of the heart's blood, or of the juice of the viscera, yield numerous colonies; pure cultivations in gelatine in test tubes can be made without difficulty directly from the heart's blood. The colonies in plate cultivations appear after two or three days as minute highly translucent, gelatinous, grey, irregularly outlined, angular patches; in the stab culture in gelatine, after two or three days, a very characteristic growth is noticed; the stab is a translucent grey line from which branch out horizontally vast numbers of fine, closely placed, gelatinous, translucent threads; in the streak culture the streak becomes visible after two to three days as a gelatinous, grey, translucent, thin band from which pass out numerous fine grey lines. The growth liquefies the gelatine very slowly; it takes generally some days before liquefaction commences, and it proceeds very slowly, the liquefied gelatine being thick like syrup, fairly limpid, but containing greyish translucent flakes. In agar mixture the growth is slow and very transparent.

Specimens made of the cultures show under the microscope, besides short bacilli, also a great many long threads more or less curved. Inoculation into mice produces the septicæmia with certainty.

This microbe is in so far interesting, as one extremely similar to it, both as to size, aspect, and its peculiar cultural characters, has been isolated by

Schütz from the spleen of pigs dead of swine erysipelas (*see* below). By its action on swine and on rodents this microbe was proved to be the real cause of the swine erysipelas, and it was also shown that its action on mice is extremely similar to that of the microbe of Koch's mouse septicæmia, just described.

E. *Human Septicæmia.*—Several microbes (micrococci, Sternberg) have been described in connection with human (traumatic) septicæmia; the staphylococcus albus liquescens, staphylococcus aureus liquescens, and the streptococcus pyogenes being mentioned amongst them. But in connection with this it must be remarked that the occurrence of these organisms in the blood-vessels of the tissues is possibly only of the nature of a secondary invasion, and may not have been the primary cause of the septicæmia, such as occurs, for instance, in hospital gangrene or in septicæmia after a *post-mortem* wound. The writer has in a case of acute septicæmia, after amputation of the mamma, seen in microscopic sections through the congested lung, liver, kidney, and mesenteric lymph glands, in the capillary blood-vessels, and extending into the surrounding more or less necrosed tissue, particularly of the liver, of the glomeruli of the kidney, and of the alveolar walls of the lung, numerous short bacilli, which formed in some places veritable emboli; their distribution clearly indicating that they stood in an intimate relation to the diseased process; but no cultures having been made, nothing further can be said of them. Chauveau and Arloing described the occurrence of bacilli in cases of gangrene, but here no culture experiments were made, although experiments on animals made it probable that these were the œdema bacilli. (On the relation of the bacillus of malignant œdema to surgical gangrene *see* a former page.) Human septicæmia is therefore a subject which at present is still awaiting solution, as far as the causing microbes is concerned; though from what has been said in a former chapter it is quite probable that some forms of human septicæmia may be due to a general invasion by the above-named micrococci. That some forms of septicæmia, not of surgical antecedent, are caused by specific bacilli is illustrated by the acute forms of disease known as ragsorters' disease, which is caused by the bacillus proteus hominis.

Ragsorters' Disease.—In a very important research carried out by Bordoni Uffreduzzi (' Zeitsch. f. Hygiene,' III., 2, p. 333) it was shown that a bacillus distantly related to the *proteus*[1] *of Hauser* (figs. 10, 11, 12), and called by Bordoni Uffreduzzi *proteus hominis capsulatus*, on account of the bacilli being surrounded by a gelatinous capsule, produces a septicæmic (acute) fatal disease in man. The disease resembles to a certain degree anthrax in man (woolsorters' disease): the lungs, trachea, bronchial glands, and mesenteric glands are congested and inflamed, the spleen is enlarged, the serous membranes and lymph glands show hæmorrhages. Cover-glass specimens made of the blood of the general circulation, the lungs, spleen, and kidney show bacilli not unlike anthrax bacilli, though there are certain well-marked differences between the two: the proteus bacillus having rounded ends, and on the whole being smaller. Sections through all organs, particularly the mesenteric and peribronchial lymph glands, show the bacilli in great numbers. The cultural characters of the proteus hominis at once show a striking difference between it and the bacillus anthracis.

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[1] Hauser's proteus is a motile bacillus occurring in putrid meat, in gangrenous wounds, and in many putrid animal substances. Two species were isolated: (*a*) proteus vulgaris, and (*b*) proteus mirabilis.

(*a*) Proteus vulgaris. Motile rods 0·6 μ thick, 1·25–3·75 in length, some short like cocci, others much longer like leptothrix threads; the threads vary in length, and are aggregated in bundles and twisted as in a cable; it grows rapidly in gelatine plates (gelatine 6 per cent.). In from six to eighteen hours the colonies are noticeable as whitish dots situated in a pit, because surrounded by liquefied gelatine. Thence rapidly extend threads and processes (swarmers), by which the growth gradually spreads over the rest of the gelatine. (Figs. 10, 11, 12.)

(*b*) Proteus mirabilis. In size, and in its polymorphous nature, the same as proteus vulgaris. The rods show slower movement, the gelatine is liquefied slower than by proteus vulgaris. The proteus mirabilis is also distinguished from the former by numerous ' involution forms,' i.e. longer or shorter threads, swollen at one end, having either at or near one end a spherical or flask-shaped knob.

The name ' proteus ' has been chosen by Hauser on account of the polymorphous nature of the microbes; some being coccus-like, others short oval rods, others again longer cylinders and threads; even vibrio-like and spirilla-like forms occur.

A third species of proteus is known as *proteus Zenkeri*: this resembles in many respects the proteus mirabilis, but does not liquefy the gelatine.

The proteus hominis does not liquefy gelatine, and grows equally well in acid, neutral, and alkaline gelatine. Further, the proteus grows very much more rapidly than the bacillus anthracis. After eighteen to twenty-four hours it forms round dots, which after forty-eight hours have much enlarged, and under the microscope appear granular, and threads can even be distinguished in them. In the streak culture it forms a white glistening waxy band; in the stab culture it grows similar to Friedländer's bacillus pneumoniæ, i.e. like a nail composed of the nailpin and nailhead; in the recent cultures the bacilli form threads; later on many very short forms are noticed. In agar cultures this proteus hominis is always well capsulated.

Experiments were made on animals with the cultures; the result of these shows a distinct difference between the proteus bacillus and the bacillus anthracis. Mice and dogs are very susceptible, rabbits and guinea-pigs are less so. In the dog the injection of culture into the jugular vein produces an acute fatal disease, very similar to that which Bordoni Uffreduzzi observed in the human subject; also the distribution of the bacilli in the organs is the same. This disease of human beings was observed to occur in persons occupied in the sorting of rags, the same disease had previously been considered as anthrax, owing to a certain similarity to woolsorters' disease and its microbes; but there can be no doubt that there are two kinds of ragsorters' disease: (*a*) real anthrax[1] due to a general and fatal infection with the bacillus anthracis, as in woolsorters' or hidesorters' disease; and (*b*) a septicæmic infection, due to the proteus hominis.

Kolb ('Arbeiten aus dem Kais. Gesundheitsamte,' VII., p. 60) describes the occurrence in the organs, but not in the blood, of persons dead from *purpura hæmorrhagica*, of thick oval rods, non-motile, chiefly occurring as diplobacteria; in gelatine their growth resembles that of the typhoid bacillus. Dogs, mice, and rabbits inoculated with cultures die in from one to three days, showing hæmorrhages in the various organs, the bacilli being abundantly present in the blood and viscera. These bacilli do not form spores.

Puerperal Septicæmia.—In a number of cases of puerperal septicæmia investigated by Dr. W. R. Smith under the writer's direction, the presence of streptococci was shown in the circulating blood. From a droplet of the heart's blood of the dead body, and from a droplet of the blood of the finger of the living, we obtained without difficulty in pure cultures large numbers of colonies of this streptococcus. Its cultural characters are in many respects similar to those of other streptococci described on previous pages. When tested by inoculation into the skin of the ear of the rabbit a distinct blush and swelling are noticed after twenty-four hours; these increase after another day or two, and then pass off, without leading to erysipelas or to suppuration; minute traces of the cultures injected into mice produce acute fatal septicæmia. The animals die in from thirty to forty-eight hours; in the blood of the heart and in that of the other congested organs—lungs, liver, kidney, and spleen—the streptococci can be demonstrated easily by cover-glass specimens and by culture. The cultures retain their virulence on rabbits and mice through many sub-cultures, even when injected in minute doses, and in this respect it materially differs both from the streptococcus of erysipelas and the streptococcus pyogenes.

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[1] Paltauf (*Wiener kl. Woch.*, 1888, Nos. 18–26) describes such cases of ragsorters' disease which are anthrax.

The writer obtained a pathogenic bacillus causing acute *septicæmia in guineapigs and mice* from the pleural exudation of mice and guineapigs that had died spontaneously from septicæmia, that is to say, in which no primary cause could be assigned, and in which the *post-mortem* appearances showed the symptoms of septicæmia—viz. great congestion of the lungs, liver, and kidney, inflamed peritoneum, pleural and pericardial exudation, the spleen dark and slightly enlarged in the mice, the intestines relaxed, congested in the mucous and serous coats, the cavity of the small intestine filled with sanguineous mucus. Inoculation of guineapigs or mice with the gelatine cultures proved fatal in the mice within one, two, or three days; in the guineapigs larger doses had to be used to produce death in a day or two. When small doses are used there is noticed already in twenty-four hours, about the seat of inoculation, a firm thickening which gradually extends into wider areas; and death ensues after several days to a week. In all cases the bacilli can be easily demonstrated in the heart's blood and in the congested organs by cover-glass specimens and by culture. In sections through the liver and kidney the bacilli are found in masses occluding like emboli the capillary blood-vessels; in the liver the central vein of a lobule and numerous capillaries leading into it are found filled with and distended by continuous masses of the bacilli, the surrounding liver tissue being in a necrotic state; in the kidney numerous capillaries between the convoluted tubes of the cortex and in the glomeruli are found occluded by the bacilli. The bacilli taken from the blood are rounded at their ends, and motile; in cultures, notably in broth or other fluids, some of the bacilli are short like cocci, others are oval, others again cylindrical; there are also numerous longer and shorter chains, which show active motility; in these chains the joints or elements are of all shapes—cylindrical, oval, or coccus-like. That all these forms belong to the same species can be easily proved by plate cultivation; for in these all colonies are of exactly the same kind.

In gelatine plate cultures the microbe forms white round flat dots, which make their appearance in the course of a day or two. These colonies gradually enlarge, their outline becoming irregular; in stab cultivation they form a white line; on the surface of the stab is a flat white plate, with a very irregular crenated outline, extending rapidly over the surface of the gelatine; in streak cultivation a white band appears with knobbed or uneven outline. The gelatine is not liquefied. No spore formation can be demonstrated, since the microbes of recent or old cultures, when dried in a thin film, or when heated to 65–70° C. for five minutes, are killed; but the culture tubes preserved at the temperature of the room remain living for many months.

In broth at 37° C. they grow very rapidly, and form a uniform turbidity during the first day; during the second and third days a copious whitish sediment appears, and the fluid contains numerous flakes and granules.

Wooldridge has shown that when these bacilli are grown in alkaline albumen solution (Brazil nuts) they form chemical substances which, when separated from the bacilli and injected into the animal, give immunity to this animal against the virulent bacilli, since a subsequent inoculation of even large doses of the active bacilli causes no disease. This is then a parallel instance to that of Roux and Chamberland, in which protection against the virulent bacilli is conferred by a previous injection of the chemical products of the bacilli.

Fowl Cholera.—This disease causes great devastation amongst poultry. The malady, well known by the researches of Perroncito, Toussaint, Pasteur, Kitt, and others, affects fowls, pigeons, and rabbits. In the fowl after an incubative period, varying between sixteen or eighteen hours to twenty-four hours, the disease declares itself by diarrhœa of fluid, greenish evacuations, great drowsiness and sleepiness of the animal. In about twenty to forty-eight hours the animals are found dead; the blood in the heart and general circulation, and in the vessels of all organs, the intestinal contents, and the evacuations teem with short, oval, non-motile bacilli, measuring 0·5–1·2 μ in length, 0·2 μ in thickness. In stained preparations they show at each end a stained granule, while the middle part is clear and unstained. On *post-mortem* examination the viscera are found greatly congested and containing hæmorrhages; the mucous membrane of the upper part of the intestine is found congested; often small hæmorrhages occur in its mucous membrane; the contents are fluid fæces; the spleen is enlarged. Fowls, rabbits, and pigeons inoculated with a droplet of the blood of a fowl dead of the disease, or inoculated with the artificial culture of the bacilli, die of the disease in from twenty to forty-eight hours, the blood teeming with the bacilli. By feeding other fowls with the intestinal contents of diseased fowls the disease can be reproduced in them. From this the conclusion is justified that also under natural conditions infection is caused by the healthy fowls picking up the contagium with the food from soil tainted with the evacuations of diseased animals (fig. 53).

The cultures of the bacilli show the following characters: In plate cultivations the colonies appear before forty-eight hours as minute yellowish white dots, irregularly outlined or round; seen under the microscope they are faintly granular discs; the centre is yellow and transparent, then follows a brown zone, and then a transparent marginal part. In stab culture the line of inoculation becomes marked as a white line made up of more or less confluent yellowish white droplets; on the surface of the stab is a small irregularly outlined plate; in streak cultures the growth appears after two or three days as a yellowish white band with irregular or knobbed outline, thin in the centre and margin, thicker and brownish in the intermediate parts; on potato the microbe grows only at higher temperatures, 28°–38° C. It grows slowly, and forms a waxy, greyish white film.

By inoculation of minute quantities, a drop of broth culture, into the subcutaneous tissue, or by feeding fowls, rabbits, mice, or pigeons with culture, the disease is easily reproduced. In guineapigs and sheep it produces a local abscess at the seat of inoculation.

By keeping broth cultures for some months Pasteur has succeeded in producing by inoculation of fowls a local œdematous inflammation; the animals became only slightly affected, but recovered and showed themselves refractory against a second inoculation. Pasteur thought that the influence of the oxygen of the air produced the attenuation; it is now proved, however, that this is not so (Kitt), but that Pasteur had impurities (accidental microbes) in his broth cultures, which at first attenuated the bacilli of fowl cholera, and as time went on altogether suppressed them; hence the broth cultures of Pasteur after the lapse of some months proved barren of all pathogenic action.

Pasteur has shown that by injection of large quantities of broth cultures, from which the bacilli of fowl cholera have been previously removed by filtration, a transitory illness can be produced, and that the animals show themselves afterwards refractory against inoculation with virulent material. Marchiafava and Celli showed that the microbe passes from the mother to the fœtus, probably owing to ruptures (hæmorrhages) in the vessels of the maternal placenta.

Eberth and Schimmelbusch ('Fortschritte d. Medicin,' Bd. VI., No. 8, p. 295) described an acute infectious disease in mustela furo—*Frettchenseuche*—showing itself chiefly as pneumonia with enlarged spleen; in the heart's blood, in the inflamed lung, the liver, and the enlarged spleen there are present numerous motile bacilli, similar in many respects to the bacillus of fowl cholera, swine fever, and Wildseuche. The cultures act very virulently on sparrows, less virulently on pigeons; fowls are refractory; in rabbits the inoculation produces only a local inflammation of a temporary character, and the same results, only milder, are produced in guineapigs.

Duck Cholera.—As such, Cornil describes a fatal infectious disease affecting ducks, which in its symptoms and causation is similar to fowl cholera; but there is this difference between them, that the disease of the duck is not transmissible to the fowl. The bacilli are, however, similar in many respects to those of fowl cholera.

On account of the morphological and cultural similarities presented by a series of pathogenic microbes—bacillus of fowl cholera, bacillus of septicæmia of rabbits, derived from human saliva (Pasteur, Sternberg), bacillus of Davaine septicæmia, bacillus of Frettchenseuche, bacillus of swine fever, bacillus of Wildseuche and others—Hueppe and also Baumgarten consider them to be identical, and they call the disease produced by them septicæmia hæmorrhagica. But this view cannot be accepted, since the experimental results produced by these different microbes in different animals are utterly different one from another; besides, this assertion is based on insufficient observation even of the cultural characters of these different microbes. Owing, however, to their being similar in size, aspect, and general character in culture, they certainly belong to the same family, but each represents a well-defined species.

Fowl Enteritis.—This is an acute fatal infectious disease affecting fowls, but not pigeons and rabbits, and by this alone its differentiation from fowl cholera is established. Besides the microbe and its distribution, the course and symptoms of the disease are quite distinct from fowl cholera. The writer has met with the fowl enteritis on a poultry farm in England, where it caused great mortality. After an incubation of three to four days, the affected fowls show diarrhœa of fluid greenish evacuations, are quiet, but never show sleepiness or drowsiness. A day or two after the diarrhœa has set in they are found dead. The mucous membrane of the intestine is found congested, but without hæmorrhage, the internal surface of the mucous membrane coated with grey or yellowish mucus, which under the microscope contains numerous leucocytes and detached epithelial cells; the liver is congested and brittle, the spleen much enlarged, the lungs normal. In the heart's blood are present relatively few bacilli, which are a little longer and thicker than those found in fowl cholera; the spleen contains the bacilli numerously, and also the vessels of the liver; the mucus of the intestine contains the bacilli in almost pure culture. In culture the microbe distantly resembles the bacillus of fowl cholera, except that its colonies are more plaque-like when growing on the surface; the microbe is non-mobile, does not form spores, and is killed by exposure to 60° C. for five minutes, as also by drying. Pigeons are insusceptible, rabbits only very slightly susceptible. By feeding of fowls with the contents of the intestine, the disease can be produced; by subcutaneous inoculation the disease can be produced, both with the blood or spleen tissue of a fowl dead of the disease, as also with artificial cultures of the microbe. In all cases the animals do not show any illness till the fourth day (this is also an important distinction from fowl cholera), or more generally till the fifth day; they suffer then from diarrhœa and are quiet; on the sixth or seventh day most of them are found dead, rarely do they survive till the eighth day, nor do they die before the fifth day. This course of the disease, the symptoms, and the pathological appearances after death are very uniform, and definitely distinguish it from fowl cholera.

By heating recent broth culture to 55° C. for twenty minutes, the writer has succeeded in so attenuating the microbe that when inoculated into fowls these become slightly ill, but they survive and prove themselves refractory against a second inoculation with virulent material. The writer has also found that continued sub-cultures on gelatine, kept up for many generations, attenuate the microbe, so that inoculations with such cultures do not produce death, but only a transitory illness, and the animals are hereby protected against a second inoculation.

Grouse Disease.—The fatal disease which affects red grouse, and known as the *grouse disease*, is an acute infectious disease, of which the chief, and we may say the essential, pathological character is that of a severe pneumonia, the lungs being greatly congested, and sometimes one or the other portion almost in a state of red hepatisation with engorgement of the blood-vessels and extravasation of blood into the air-spaces; the serosa and mucosa of the intestine show patchy redness; the liver is greatly congested and dark; the spleen is not enlarged. In the diseased lung and in the liver there occur in the vessels and in the extravasated blood numerous bacilli singly, or more commonly in larger or smaller groups, sometimes forming emboli in the capillary blood-vessels. These bacilli belong to one and the same species; they are motile, either oval or even coccus-like, and some few are rod-shaped. By cultivation on gelatine they can be easily obtained in numerous colonies from the sanguineous juice of the lung and liver; only in few cases are they to be seen in the heart's blood, both in cover-glass specimens and in culture. The morphological characters of the microbe are shown in figs. 47–49.

The microbe when examined from a cultivation is often rod-shaped—more often than in the tissue of the grouse. The motile forms are common in recent cultivations; in cultivations some days old most of the microbes are non-motile. Cultures inoculated into mice and guineapigs produce general infection, and speedy death, mice being more susceptible than guineapigs; in both animals the disease produced is a double-sided pneumonia. Sparrows are also susceptible, but less so than the common bunting and yellow-hammer, which birds are highly susceptible; also in these the disease produced is a double-sided pneumonia. The microbe is present in numbers in the heart's blood, but particularly in the diseased lung.

Fowls, pigeons, and rabbits are insusceptible to the disease. These two species—the bacillus of fowl enteritis and the bacillus of grouse disease—owing to their size and cultural characters, also belong to the group or family of bacilli mentioned on a former page, which include fowl cholera, septicæmia of rabbit, Frettchenseuche, swine fever, and Wildseuche.

Swine Erysipelas (Mal rouge, Rouget, Red Soldier).—An acute infectious disease, to which swine are very susceptible, and of which about 60 per cent. of those attacked succumb. The affected animals are quiet, their voice is hoarse, and the temperature is much raised; on the skin of the neck, chest, abdomen, and thighs extensive red patches of swollen œdematous skin are noticed; under convulsions—occasionally paralysis of he hind extremities—the animals die in from twelve hours to three or four days after the first symptom. On *post-mortem* examination hæmorrhage is found in the affected patches of the skin, the lymph glands are swollen and much congested, the peritoneum is inflamed, the mucous membrane of the intestine is much injected and œdematous, the Peyer's glands are swollen, the spleen and liver are much congested and slightly enlarged.

The blood of the heart, and particularly the juice of the lymph glands and the spleen, contain fine bacilli very similar to those of Koch's mouse septicæmia (Schütz), 0·6–1·8 μ long. In microscopic sections through the liver, spleen, kidney, and lymph glands the bacilli are easily demonstrated in the capillary blood-vessels, either isolated between the blood-corpuscles or enclosed in the swollen leucocytes. As regards cultural characters, they completely resemble those of the mouse septicæmia (Koch) described on a former page. (p. 100)

Swine fed or inoculated with the blood or tissues of a swine dead of the disease become also affected. Mice[1] and pigeons are very susceptible to the disease; guineapigs and fowls are refractory; rabbits show generally only a local effect; mice die in two or three days, pigeons in three to four days; in all, the blood of the general circulation and of the organs contain abundantly the bacilli. In the pigeon numerous white blood-corpuscles in the vessels of the viscera are filled with the bacilli.

Pasteur has shown that the virus in its passage through a series of pigeons increases in virulence, both as regards the pigeon as well as the pig; on its passage through a series of rabbits, it increases in virulence as regards the rabbit, but decreases in virulence as regards the pig. Pigs inoculated with blood of the last rabbit of the series become ill, but recover, and are then found protected against the virulent disease.

Swine Fever.—This disease prevails largely in this country; in America it is known as hog cholera, on the continent of Europe as swine plague. It is a highly infectious disease, spreading from animal to animal by way of air, food, water, the lungs and bronchi and the intestines being the chief seat of the disease, and containing the virus. The infection is, under natural conditions, attributable to the virus being derived from and spread by the expectoration of the lungs and the evacuations of the bowels. Both by feeding, respiration, and by inoculation with particles of the diseased lung and intestine, the disease is easily reproduced in healthy swine. After an incubation period varying from between two days and six to seven days the animals are quiet and refuse food, the body temperature shows slight rise, red patches of a transitory nature are noticed on the belly and thighs; cough and occasionally diarrhœa of fluid evacuations soon declare themselves; the inguinal lymph glands appear enlarged. In severe cases the diarrhœa increases, the fever continues, the cough becomes more pronounced; this state lasts for a few days, seldom more than a week, and under general prostration the animal succumbs. In a large percentage (50) of cases the animals recover. In a considerable percentage of cases, the disease is very mild and diagnosed only with difficulty: the rise of temperature is but slight and transitory, lasting only a day or two; the animals feed fairly well, and have a slight cough occasionally and at long intervals; the inguinal glands are slightly enlarged. These symptoms are so slight and so little marked that it requires careful examination to diagnose the disease; nevertheless, on auscultation of the chest, distinct lung disease may be recognised. On *post-mortem* examination of such slight cases the disease of the lung is easily confirmed.

In the well-pronounced cases terminating in death the *post-mortem* examination shows the following appearancees: the lungs of both sides show severe extensive lobar pneumonia, involving sometimes the greater part of the lung; in recent cases the lobules show all stages between congestion (punctiform hæmorrhages) and hepatisation; the lobes that are longer affected show more consolidation, and the older this is, the more grey, solid and necrotic, dry and friable, is this part of the lung; the septa between the lobes are œdematous and well marked; the bronchi and trachea contain grey and sanguineous muco-purulent matter; the endocardium of the left, and occasionally of the right ventricle near the atrio-ventricular valves, and also these latter show patchy and punctiform hæmorrhages; the liver is congested, and occasionally shows dark red patches, due to hæmorrhage; the spleen is enlarged and dark; the colon and cæcum, particularly the former, contain punctiform hæmorrhages; in many cases also prominent, round or oval isolated, or in severe cases, more or less confluent ulcers (necrosis), showing an infiltrated base, and being stained greenish black by altered bile pigment; between a few small round ulcers near the ileo-cæcal valve to very numerous extensive ulcerations, comprising occasionally extensive areas of the mucous membrane of the cæcum and colon, all intermediate stages can be noticed (*see* Klein, in the 'Report of the Medical Officer of the Local Government Board for 1878).'

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[1] Mice die with congested and enlarged spleen and greatly congested lungs; the intestines are relaxed and filled with sanguineous mucus; the kidney and liver are enlarged and congested.

In the stomach hæmorrhagic patches can occasionally be seen. The lymph glands along the bronchi, and the mesenteric and pelvic glands, are swollen, juicy, dark red, in part or wholly, and contain hæmorrhages. The peritoneum is inflamed, and on its surface are clumps of solid lymph composed of leucocytes. Owing to the lungs and intestines being found constantly affected, the disease has been designated by the writer pneumo-enteritis; but in Germany (Schütz) and in America (Salmon), it is asserted that the above disease is really two—one a disease of the lung, the other of the intestine; but from experiments made on a large scale with diseased lung, and with diseased intestine, and from the *post-mortem* appearances in well-defined localised outbreaks that the writer has made, he is of opinion that this division cannot be maintained, but that the swine fever in this country is one single disease, viz. pneumo-enteritis. Microscopic examination of the lung and intestine shows that the disease really commences with congestion, stasis, and hæmorrhage, leading to infiltration and necrosis of the affected parts. The cause of the disease is a bacillus, which, in the affected tissues of the pig, appears, as a rule, as a short rod, often constricted in the middle; in fluid cultivations (broth) and in animals (rabbits, mice) as a cylindrical rod, singly or in dumb-bells, occasionally growing to considerable length, and forming longer or shorter chains; but there can be always found short forms almost like oval cocci, rods, and cylindrical bacilli. Cover-glass specimens and cultures of the lung, spleen, lymph glands, and the sub-mucous tissue of the affected intestine, demonstrate the presence of the bacilli. These bacilli are motile, though the motility is observed in a minority; in cultivations in broth, gelatine, and agar, many of the bacilli are motile during the first few days, but lose their motility later.[1]

In gelatine plate cultivations the colonies, when first noticed, i.e. after about twenty-four hours, are greyish dots; in two to three days they are conspicuous as whitish round specks of about the size of a large pin's head; in transmitted light they appear brownish, granular. In stab cultures, the stab of inoculation becomes marked as a white line made up (when seen under a glass) of minute globules closely placed side by side; on the surface of the stab is a small irregularly outlined whitish patch. In streak culture the line of inoculation is occupied in a few days by a grey band, knobbed or crenated in its outline. On agar the growth (at 37° C.) is a greyish brown smeary film, rapidly spreading over the surface of the agar. In alkaline broth at 37° C. uniform turbidity is produced; after a few days a voluminous greyish white precipitate is noticed at the bottom of the tube. No distinct pellicle is formed on the surface.

Inoculation of swine with cultures produces the disease, but this does not lead to death, and such animals after recovery show themselves refractory against inoculation with material of the diseased lung or intestine.

Inoculations into guineapigs with material from the diseased swine produce at the seat of inoculation hæmorrhagic infiltration and thickening, sometimes leading to death in two or three days; often, however, the thickening passes off in a week or so; cultures injected subcutaneously in guineapigs produce thickening at the seat of inoculation but rarely death.

Inoculation into mice of minute particles of material of the diseased lung, or intestine, or of gelatine or broth-culture of the bacillus of swine fever, causes disease and death in four to eight days: the spleen is found enlarged and dark; the liver is mottled with grey dots, streaks, and patches of necrotic tissue; the peritoneum is inflamed, and so are the kidneys, as also both lungs. Cover-glass specimens and cultures from the heart's blood, liver, kidney, and particularly the spleen, demonstrate the presence of the bacilli in large numbers (*see* fig. 56). Among the bacilli in the spleen, numerous long cylindrical rods can be seen. In the kidney many of the capillaries of the glomeruli are plugged by the bacilli, so also in the liver.

In the rabbit, inoculation produces disease and death in a few days: the spleen is slightly enlarged, the lungs are inflamed, the kidney is much congested in the cortex. Here also the bacilli can be easily demonstrated in the heart's blood, the liver, and the kidney; in this latter many Malpighian corpuscles show the capillaries of the glomeruli plugged with masses of the bacilli.

As we mentioned above, although the microbe of Davaine's or Koch's septicæmia in the rabbit, the microbe of fowl cholera, and others (Frettchenseuche, Wildseuche, fowl enteritis), and the microbe of swine fever are in many microscopic and cultural respects similar, it is erroneous to suppose that they are identical; there are sufficient differences amongst them in cultural respects alone to distinguish between them; but in their action on animals they are distinctly different. The microbe of Davaine's or Koch's septicæmia produces a disease in rabbits, and particularly in mice, different from that of the microbe of swine fever; the microbe of fowl cholera and of rabbit septicæmia act differently on swine from that of swine fever. But all these, no doubt, belong to the same group or family of species as mentioned above; their microscopic and cultural characters, and to a certain degree also their action on animals, being similar though not identical.

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[1] It is curious to find Flügge (*Die Microorganismen*, 2nd edition, 1886, p. 249) maintaining that, because the writer stated that the bacillus of swine fever is motile like a bacterium termo, he could not have had before him the bacillus of swine fever. Flügge evidently considers swine erysipelas and swine fever as one disease.

A disease amongst cattle (Rinderseuche) and horses, and amongst deer (Wildseuche), manifesting itself in diffuse pneumonia and hæmorrhagic enteritis, but without necrotic change (consolidation and dryness) of the lung, and without ulceration of the intestine, was first recognised by Bollinger. Kitt has shown that this affection is caused by a bacillus in many respects (morphological and cultural) similar to that of fowl cholera, rabbit's septicæmia, and swine fever; and Kitt and Hueppe maintain, indeed, the identity of all of these microbes; but the evidence brought forward by them is not satisfactory. True, rabbits inoculated with the microbes obtained from Davaine's septicæmia, fowl cholera, swine fever, or Wildseuche succumb under the symptoms of Davaine septicæmia; it is likewise true that pigeons inoculated with cultures derived from either of these diseases die with symptoms similar to fowl cholera; still a great deal remains yet to prove the identity, as regards the action on swine, of the bacteria of rabbit's septicæmia, fowl cholera, and Wildseuche. To mention only one series of difficulties. Fowls, as mentioned above, are highly susceptible to the microbe of fowl cholera, but they are insusceptible to the microbes of swine fever or Wildseuche.

Billings (' Texas Fever,' Lincoln, Nebraska, 1888) describes a species of small motile bacilli, closely related to the bacilli of swine fever, both as to morphology, cultural and pathogenic characters, as the cause of the cattle plague in Texas and other southern parts of the United States.

Charbon symptomatique.—This disease, affecting young cattle and sheep, occasionally produces great mortality amongst them, particularly amongst the former. Owing to its involving chiefly one of the hind extremities in the form of a large subcutaneous tumour, which, on incision, shows a quantity of sanguineous, discoloured, almost black fluid, the disease is called *quarter ill* or *black leg*. Owing to its slight resemblance to anthrax (large tumour containing serous sanguineous fluid) it is called in France *charbon symptomatique*; in Germany it is called *Rauschbrand*, on account of the emphysematous nature of the tumour, and on account of the gangrenous nature of the infiltrated tissues. The disease, when it appears, rapidly spreads amongst young cattle and sheep, seldom amongst horses; it is unknown amongst swine or poultry. The animals affected are quiet, do not feed, and show high temperature; on one or other of the quarters—generally one of the hind—there appears a large diffuse swelling, on account of which the animal is lame and cannot move that extremity. In the course of thirty-six to forty-eight hours death takes place. On *post-mortem* examination the tumour is seen to be located subcutaneously; here the connective and muscular tissues are dark, almost black, gangrenous, and contain a large quantity of sanguineous serum and a large quantity of gas bubbles (said to be CO_2 and methane). The infiltration with sanguineous serous fluid extends for some distance into the adjacent parts of the muscular tissue; there is congestion of the liver, spleen, kidney, and particularly the subcutaneous lymph glands: these, beginning from near the tumour, are found swollen, dark, and on incision a sanguineous fluid oozes out from them. The spleen is only very slightly enlarged. Cover-glass specimens of the subcutaneous and muscular infiltration at or near the tumour, particularly of the subcutaneous lymph glands, show in considerable numbers small motile bacilli 3–5 μ long, and about 0·5 μ thick: they are rounded at their ends, and some contain terminally a bright oval spore; others possess a terminal enlargement without a spore (Bollinger, Arloing, Cornevin, and Thomas).

Immediately after death the bacilli are not easily demonstrable in the heart's blood, being present only in small numbers, though they can be shown to be present in the liver, spleen, and kidney, but always more numerously if some hours are allowed to elapse after death.

The exudation of the tumour or of the surrounding muscular tissue injected subcutaneously into guineapigs in comparatively large quantities (½–1 Pravaz syringe) produces the same kind of emphysematous gangrenous infiltration with sanguineo-serous exudation at or near the place of inoculation; the animals die in from twenty-four to sixty hours, the internal viscera show great congestion; in the subcutaneous tumour, in the blood of the heart, and in the juice of the viscera, the bacilli can be easily demonstrated; in the blood and viscera they are fairly numerous if some hours have elapsed after death (*see* fig. 71).

If only a drop or two be injected, the guineapigs, though they become affected with the local disease, do not succumb, but show themselves refractory against infection with large quantities, such as in control animals would invariably produce death. Rabbits are only slightly susceptible.

Arloing, Cornevin, and Thomas have brought to light various important facts connected with the action of the bacilli. These authors cultivated the bacilli in broth, but they found that the bacilli grow best in chicken broth, glycerine and sulphate of iron, provided oxygen (air) is excluded; they are, therefore, true or obligatory anaërobic bacteria. They grow well in grape sugar gelatine, but must be inoculated into the depth of it. The character of the growth is similar to that produced by Koch's malignant œdema bacillus, except that the former forms fewer gas bubbles, grows much faster, and afterwards does not form such voluminous fluffy masses in the liquefied gelatine as the bacillus of malignant œdema.

Arloing, Cornevin, and Thomas have shown that if small quantities of the fluid of the natural tumour be injected subcutaneously into cattle, only a local, though typical tumour is the result; the animals recover, and then are possessed of immunity against further inoculation with otherwise fatal doses.

Further, they found that three to five drops of the tumour fluid injected into the vein of cattle—but without inoculating the subcutaneous tissue around the vein—produce only a transitory febrile disturbance; the animals quickly recover, and show themselves refractory against subcutaneous fatal doses. A safe mode of protective inoculation used by these observers successfully on a large scale is this: The tumour fluid is rapidly dried at 32–35° C., then it is rubbed up with water, and heated to 100° C. Another lot is treated in the same way, but heated only to 85° C.; the first lot represents a first vaccine (*premier vaccin*), the second lot a second vaccine (*deuxième vaccin*); both can be dried and sent to distances; when required for use the dried matter is rubbed up in 100 parts of water, and of this 1 c.c. per animal is subcutaneously injected. The *premier* (weaker) vaccine must be used first; after the lapse of about ten or twelve days the *deuxième* (stronger) vaccine is injected. Animals thus twice vaccinated proved themselves completely protected against a fatal and virulent dose taken from the natural tumour.

Though there exists, both as regards the pathology and the microbes, a certain resemblance between the malignant œdema and the charbon symptomatique, this resemblance is only superficial, and there can be little doubt that the two diseases in their pathology, in their microbes, and their transmissibility or non-transmissibility to certain animals are *totally different* diseases.

CHAPTER XV

ANTHRAX

Anthrax is a fatal acute disease affecting naturally sheep, cattle, horses, goats, deer, and man. A conspicuous symptom on *post-mortem* examination is the dark, greatly congested and enlarged spleen, the enlargement amounting to three or four times the natural size of this organ; hence the name Milzbrand, or splenic apoplexy. In sheep and cattle there occur hæmorrhagic exudations under the skin of various regions, the exudation forming tumours of a dark to black gelatinous nature; hence the name anthrax, charbon: in human beings affected by accidental inoculation of the skin, a large pustule or swelling with black core is found; hence the name malignant pustule, or carbuncle. This disease, when naturally contracted by sheep, cattle, goats, and horses, declares itself by rise of temperature, and rapid loss of muscular power; the animals are very quiet, do not move and do not feed; twenty-four hours after, or even sometimes before, they are found dead. In some virulent epidemics of anthrax the animals have been seen to die in a few hours after the first symptoms set in; such cases are known as fulminating anthrax. On *post-mortem* examination, gelatinous sanguineous tumours are found in various parts under the skin; the spleen is dark, soft, full of blood, and several times its natural size; the liver, lungs, kidney, stomach, intestines and lymph glands are greatly congested, and often show hæmorrhages; the serous membranes are congested and show petechiæ; the blood has not much tendency to coagulate. Examined under the microscope, in all these organs the capillaries and veins are found distended and filled with blood; in many places, e.g. in the alveoli and bronchi of the lung, in the spleen, in the vessels of the liver, kidney, omentum, intestinal mucous membrane, and subcutaneous tissue, there are ruptures of the capillaries and small veins, in consequence of which blood *en masse* is effused into the surrounding tissue. In sheep, goats, horses, and cattle there are always sanguineous effusions from the stomach and lungs by the mouth and nose, from the kidney and bladder by the urethra, and from the intestine by the anus.

Brauell and Davaine, about twenty-five years ago, showed that in the blood of the general circulation, in the spleen, and in the subcutaneous effusions there always occur straight, non-motile rods (bacteridiæ of Davaine), which were considered to be probably connected with the cause of the disease. Zürn, Klebs, and others have shown that the blood of animals dead of anthrax—which blood is very virulent when inoculated into fresh animals, for it produces the fatal disease—fails to produce the disease after the rods are removed from the blood by filtration.

Koch in 1876 carefully studied these rods, and has shown that they are bacilli, which except for their non-motility, and certain small differences—to be mentioned presently—grow and multiply, and form threads and spores after the manner of the bacillus subtilis of Cohn. Koch studied directly under the microscope bits of spleen removed from a mouse dead of anthrax after inoculation, and he saw how the rods elongate and divide, how they gradually grow out into smooth threads in which after a day or two bright glistening oval spores appear, how in the meantime the threads swell up and disintegrate and the spores become free; he further observed how such spores germinate again into the bacilli (*see* a former chapter), how these again multiply by division, grow into threads, and finally again form the bright oval spores. With the spores, by inoculation of mice and guineapigs, he readily produced anthrax, and death in thirty-six to forty-eight hours; the spleen of these animals was found greatly enlarged, dark, full of blood, every drop of the blood of the spleen and the general circulation teeming with the bacilli. In microscopic sections he found the capillary blood-vessels in many organs almost filled with the bacilli.

The bacilli are found in the blood and spleen of every animal dead of anthrax, more numerously after than before death, though there is no difficulty in demonstrating them an hour or so before death; a few hours after death they are found as a rule in the blood of the spleen in great crowds, and to a lesser degree in that of the general circulation.

In fine sections through the spleen a very striking difference is noticed between the pulp and the Malpighian corpuscles, the former being full of the bacilli, the latter containing them either not at all or only sparingly.

The bacilli examined fresh are non-motile rods, homogeneous-looking, more or less truncated at their ends; their length differs very greatly from cylindrical rods to short, uniform threads or chains of bacilli, the latter 5–20 μ in length; their thickness amounts to 1 μ or a little over. There exist certain differences in so far as most of the bacilli in the blood and spleen are shorter when death ensues rapidly than when it ensues late, say after three days or later; in the guineapig dead from inoculated anthrax, in between thirty-six and forty-eight hours, the bacilli are longer than in the sheep dead in the same time; the bacilli are also a little thicker in the guineapig than they are in the mouse or sheep. Koch was the first to show in cover-glass specimens of the blood or spleen juice (dried and stained) that the bacilli, though in the fresh state they appeared as uniform cylindrical rods, are really made up of short, cubical, or more or less elongated protoplasmic elements, all with square cut or even with concave ends,[1] and this appearance has a certain diagnostic value, since it is not generally seen, or at any rate it is not so marked in other bacilli; but it must be remembered that the above character is not invariably shown by the anthrax bacilli; in the mouse many bacilli do not show it, since many of the longer forms are made up, not of short cubical, but of long cylindrical elements, and further the writer has seen bacilli (e.g. the bacillus filamentosus) in which the above appearance was as pronounced as in typical anthrax bacilli.

The longer bacilli or their chains, taken from an animal dead of anthrax, or from an artificial culture, and examined in dried and stained cover-glass specimens show within a common sheath cubical or rod-shaped cylindrical, square cut, stained masses of protoplasm; these are the real bacillary elements; the cylindrical elements often show a middle constriction more or less deep, indicating the division into two elements: these will be of course cubical if the original cylindrical element is short; between adjoining elements a transverse septum can be occasionally seen. In specimens made of artificial cultures these appearances are more easily noticed. since they are more pronounced; in some anthrax-threads of cultures all elements constituting a thread are separated one from another by a transverse septum.

The mode of infection of animals under natural conditions is effected by their grazing on land previously infected with the spores of bacillus anthracis. As mentioned above, in sheep, goats, cattle, and horses there are always discharges from the mouth, nose, anus, and urethra, full of the bacillus anthracis: these discharges soak into the soil where the animal falls dead of anthrax. If the superficial soil is favourable for the multiplication of the bacilli and the formation of the spores—and most soil in the spring and summer, owing to temperature and an abundance of proteid nutritive material and on account of its containing air, is favourable both for the multiplication of the bacilli and for the spore-formation, particularly when owing to the presence of a small amount of lime the reaction of the superficial layers is only neutral or even slightly alkaline—very soon a large and abundant crop of spores will be the result. Add to this the circumstance that when an animal falls dead of anthrax in a field, it is not at once buried; nor is the earth surrounding the animal and saturated with the infective discharges disinfected; but, on the other hand, the animal is generally carted away to a distant point in the field, perhaps a corner where the dead animals are buried; and in this way blood and fluids full of the bacilli are dropped about; besides, before being buried the animal is generally skinned, and hereby a lot of blood full of the bacilli is smeared about the ground. Every copious watering, as by the spring and autumn rains, will subsequently distribute the spores over wide areas; these spores, owing to the favourable temperature during the spring, summer, and early autumn, will be able to germinate, and by multiplication of these bacilli to produce an abundance of further bacilli in which spore-formation will again proceed. Thus within a few seasons an amount of infective spores will be produced capable of giving infective power to large areas. Sheep or cattle feeding or grazing on such land are liable to infect themselves with the spores. Feeding on bacilli alone does not produce infection, as has been proved by numerous experiments, but spores may pass unscathed through the stomach and be absorbed into the system, and thus produce anthrax; likewise inhalation of spores produces anthrax. Water infected with spores of anthrax from such a field, or from other sources, is infective for sheep and cattle.

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[1] The illustrations given by Koch and others as to the concave ends of the bacilli seen in dried and stained cover-glass specimens, though of diagnostic value, are not pre-formed, but are due to the methods employed; in sections through the properly prepared or fresh tissues the bacilli do not show this appearance.

Infection through cutaneous inoculation (abrasions, ulcers, &c.) is not common in sheep or cattle, though in horses, infection and local malignant pustule is not uncommon. Men that have handled the carcases of sheep, cattle, and goats dead of anthrax have, by subsequently grooming horses, been known to inoculate these latter with anthrax, in consequence of which malignant pustule has been produced at the seat of inoculation, leading occasionally, if not cut out, to general fatal infection with anthrax.

Bollinger has shown that infection of animals may be effected by the instrumentality of flies: these, having been previously sitting on the carcase of an animal dead of anthrax, carry matter (blood, oral, nasal, and other discharges), containing the bacilli anthracis, to another animal on which they alight, particularly on sores or abrasions of such an animal, and hereby inoculation with the anthrax bacilli may be easily effected.

Pasteur maintained that in the body of sheep, dead of anthrax and then buried, the bacilli form spores, which latter in the course of years may be brought up to the surface by earthworms, and become a source of infection for animals grazing here. Koch has shown that the bacilli anthracis do not form spores unless well exposed to air; they do not form spores within the body of an animal dead of anthrax. The statement of Archangelski, that in the blood of the living animal affected with anthrax there occur 'spores,' which under certain conditions of cultivation can be shown to divide and to multiply as spores, cannot be accepted as correct, as the writer has shown in his Report to the Medical Officer of the Local Government Board for 1882. Further, the writer has there shown (*ibid.* 1882) that if an animal dead of anthrax is buried or left unopened, all bacilli anthracis in the blood and organs of such an animal degenerate in the course of several days, so that even large quantities of blood or spleen taken after this period and injected into a suitable animal do not produce anthrax. Mice and guineapigs dead of anthrax are buried in earth or left unopened, after a week the spleen is used for inoculation of mice and guineapigs, but it fails to produce anthrax (*ibid.* 1882); [1] the bacilli, not having been able to compete with putrefactive organisms, and no free oxygen being present, have all degenerated.

Anthrax in man takes place after inoculation of a cutaneous wound by persons handling the carcases of animals dead of the disease, e.g. grooms, shepherds, cattle drovers, butchers, knackers, &c. The place of inoculation becomes a large, more or less firm, discoloured, painful tumour after sixteen to twenty-four hours; in its centre, i.e. at the point of inoculation, there is a black core; the connective tissue of the tumour is greatly infiltrated with serum and blood, the whole infiltration being of a sanguineous, gelatinous nature. In the exudation there are numerous bacilli anthracis; the infiltration and phlegmon gradually extend into wider areas, with constitutional disturbance, i.e. fever and pains all along the infected part. In few cases a general infection, i.e. invasion with bacilli from the carbuncle, takes place; in these cases the bacilli are found in the blood, but only rarely does a fatal result ensue.

Another mode of infection is that with general anthrax, and this in a large percentage of cases leads to a fatal issue; in all cases it is associated with severe febrile disturbance; the general infection occurs either by the alimentary canal or by the respiratory tract; in both instances the bacilli anthracis enter in the form of spores. In woolsorters' disease, in anthrax of ragsorters, and in anthrax of hide-sorters it has been conclusively shown by Mr. Spear (*see* his Reports to the Medical Officer of the Local Government Board for 1881 and 1882) that in one case the dust of infected wool, in the other the handling of the infected hides, was the source of the contagium. In localities in which anthrax occurs almost endemically amongst sheep or goats, e.g. certain parts of Russia, Armenia, Turkey in Europe and Asia, the fleeces of animals dead of anthrax are preserved, their wool being as a matter of course smeared with blood and other excretions containing the bacilli anthracis. In these materials there is every opportunity for the bacilli to form spores, which resist drying and other processes fatal to the bacilli as bacilli. These spores remain adhering to and buried within the wool. The wool brought to a factory is first of all turned out from the bales and sorted; hereby a large amount of dust is separated which during the sorting and other subsequent processes is sure to become mingled with, and suspended in the air of the work-rooms; the workers in such rooms are therefore particularly liable to infect themselves with the spores, either by mouth and alimentary canal, or by the respiratory organs. The disease which ensues has been carefully described by Mr. Spear: it resembles in a marked degree the general virulent form of anthrax in animals, the congestion and enlargement of the spleen, the extreme congestion of the lungs, and the hæmorrhage in the air cells and bronchi, the congestion of, and hæmorrhage in other viscera being the most prominent symptoms. The blood of the general circulation and all the vessels of the organs contain the bacilli anthracis. The water which is used for the washing of the infected wool has been known to contain the spores and to produce anthrax in cattle that had drunk it. Hides coming from a country where anthrax occurs amongst cattle (China, Russia, Turkey) are in the same position as wool; when the hide is taken off from the animal that has died of anthrax there is also on the inside of the hide a large amount of blood smeared over and adhering to it, besides there is blood naturally contained in the subcutaneous tissue. All this blood teems with the bacilli anthracis. Such hides are exposed to drying, but as this process always takes a good many hours there is every opportunity for the bacilli, that are exposed to the air, to form spores. As the subcutaneous tissue dries, these spores become well fixed on and in it; the drying does not, of course, interfere with the life of the spores. In addition to this, the hides are subjected to a process of curing, i.e. certain chemicals perfectly harmless to the spores are coated over the inner surface of the hide by which the spores become only more shielded from being lost. So that when such hides are afterwards handled, dust and particles containing the spores coming off from them readily produce infection either through the alimentary canal or through the respiratory organs, or a local carbuncle is produced by inoculation. Infection through the alimentary canal of human beings generally declares itself by prominent symptoms on the part of the alimentary canal, *mycosis intestinalis*: great congestion, inflammation, and hæmorrhage of the bowels; congestion, inflammation and hæmorrhage of the mesenteric lymph glands. The intestinal contents, the lymphatics of the intestine, and the mesenteric glands contain abundantly the anthrax bacilli. A general invasion of the system and fatal anthrax is the result.

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[1] Esmarch in 1889 arrived at the same results (*Zeitschrift f. Hygiene*).

Fatal anthrax in ragsorters has been observed several times—*see* Paltauf (‘Wiener klin. Wochenschrift,’ 1888, Nos. 18–26)—but not all acute infectious diseases contracted by the sorting of rags is anthrax, as has been proved by the research of Bordoni Uffreduzzi mentioned on a former page in connection with septicæmia in man caused by the proteus hominis.

While sheep and goats, cattle and horses, white mice and guineapigs, are easily infected with anthrax by inoculation, rabbits, although fairly easily susceptible to it, are a little less so than mice and guineapigs; pigs are difficult to infect, though they can be infected (Crookshank); adult rats, dogs, and cats are almost insusceptible; fowls in the healthy state are insusceptible, but Pasteur found that by cooling their bodies they can be infected with fatal anthrax. Chauveau has shown that also amongst sheep those of Algiers are to a large extent refractory against anthrax.

By subcutaneously inoculating sheep, cattle, and guineapigs with a drop, or a fraction of a drop, of the blood of sheep or cattle dead of anthrax, or with virulent culture of anthrax bacilli, there is found at the seat of inoculation in from sixteen to twenty-four hours a tumour due to œdema; after inoculation with spores somewhat later. This increases during the next day to a very considerable degree and involves extensive areas of the subcutaneous tissue. In cutting into the tumour it is seen that it is due to a gelatinous infiltration of the connective tissue and slight hæmorrhage, the infiltration abounding in bacilli anthracis; from the gelatinous infiltration, on incision, clear serum containing bacilli and a few red blood-corpuscles easily and spontaneously separate; the infiltration has no odour. The temperature of the body is greatly raised, to 41° C. The animals die in between thirty-six and fifty-four hours. Some hours before death the temperature rapidly falls to 36 or 35° C. The animals are weak, and appear paralysed. On *post-mortem* examination the spleen is always found greatly enlarged, the lungs, liver, kidney, and peritoneum much congested, and often showing hæmorrhagic spots; the blood has not much tendency to coagulate. In the heart's blood, the spleen, and in all vessels of the organs the anthrax bacilli are found in great numbers. The inoculated disease is therefore identical with the one occurring naturally.

There exist considerable differences in the degree of virulence shown on inoculation of different animals with the blood of anthrax derived from different sources. Thus blood of mice that die from typical anthrax within forty-eight hours produces on inoculation typical and fatal anthrax in mice, guineapigs and rabbits, but in sheep and cattle it does not do so; it produces a local œdematous tumour with fever; but this, after two to three days or later, again disappears and the tumour gradually vanishes. In sheep the effect is more severe than in cattle, but such animals are refractory to a second inoculation with virulent anthrax, which otherwise in healthy sheep would produce fatal anthrax. Blood of guineapigs dead of typical anthrax within forty-eight hours, or so, inoculated into mice, guineapigs, rabbits, and sheep, produces as a rule local tumour and general fatal anthrax in forty-eight hours or so; but in cattle a local tumour follows, sometimes severe and extensive, with constitutional disturbance, but as a rule no fatal result, and such animals are refractory to a second inoculation with virulent material. Blood of sheep and of cattle dead of typical anthrax produces on inoculation in all animals typical and fatal anthrax. So that we conclude from this that the virulence of the bacillus anthracis growing in the body of a mouse is of a lesser degree than that derived from the body of a guineapig; that the virulence of the bacillus anthracis derived from the body of a guineapig is of a lesser degree than that of the sheep or cattle; further, to produce fatal anthrax in the mouse, anthrax of a lesser degree of virulence than for the guineapig is sufficient; for this, again, a lesser degree of virulence than for the sheep, and for this again a lesser degree of virulence than for cattle. Or, to put it in a different form: anthrax bacilli from a virulent source, say of sheep or cattle, on their passage through the mouse suffer attenuation of virulence, but on their passage through a sheep, or still more through the body of cattle, do not lose in virulence.

That human beings contract local anthrax (carbuncle) by inoculation from blood of sheep, cattle, or horses is well known, and has been mentioned above; that human beings contract general anthrax from spores of anthrax of sheep or cattle is proved by woolsorters' and hidesorters' disease, but there is no record that anthrax, local or otherwise, has been contracted by human beings from mice or guineapigs in the very many instances in which in laboratories the bodies of these animals dead of anthrax have been handled. The writer has seen a good many instances in which the *post-mortem* examination of the bodies of these animals had been carelessly performed by assistants and others, who sometimes had abrasions and wounds on the fingers, yet no infection has resulted from it.

Various degrees of virulence are also noticed of artificial cultivations of anthrax, though all yield growths which in morphological and cultural characters do not differ one from another. Thus anthrax bacilli grown for some weeks at 37° C. on distinctly alkaline agar are less virulent than when grown on neutral or faintly alkaline agar or on potato; anthrax bacilli grown in faintly alkaline broth or on neutral or faintly alkaline gelatine are more virulent than when grown on distinctly alkaline gelatine; the spores found early in cultures of broth and gelatine cultures are more virulent than the bacilli of the same cultures. The different degrees of virulence are estimated by this: cultures that kill every guineapig of about the same age (young animals are more susceptible than old ones) with typical anthrax within forty-eight or fifty hours are virulent; if only a percentage of them die within that time, others during the fourth or fifth day or later, the virus is of a lesser degree ; further, the less resistant to perchloride of mercury or other agencies the bacilli or spores are, the less virulent they are found on inoculation into guineapigs, and the less virulent also their sub-cultures. More than that, the less virulent the anthrax is at starting, the less virulent (*cæteris paribus*) also the bacilli when taken from a guineapig infected with such culture (*see* the writer's Report to the Medical Officer of the Local Government Board, 1885 [1]).

The bacillus anthracis offers some very characteristic features in cultivations. In gelatine plate cultivations made of the blood (previously well diluted with neutral salt solution or broth, on account of the large number of bacilli, present in the blood), already after twenty-four to thirty-six hours the first signs of colonies can be made out in the form of translucent grey angular dots ; after forty-eight hours to three days they are conspicuous by their size, and by their margin being distinctly made up, to the naked eye, of filaments, either straight or bending like loops. Under the microscope the filamentous nature of the colonies is distinctly seen ; the filaments looked at under a magnifying glass are more or less in bundles twisted like cables, and extending sometimes like radii from a centre ; at the margin this is particularly conspicuous. At the same time the colony is seen to be sunk in the middle, being situated in a slight depression of the gelatine due to commencing liquefaction. Looked at obliquely, the gelatine looks pitted by the colonies. As growth proceeds the colony enlarges, the marginal loops and bundles of twisted filaments project more or less irregularly, some project for longer, others for shorter distances, sometimes not much beyond the margin of the colony, and the gelatine surrounding the colony becomes more and more liquefied, but remains clear in the liquefied part. In stab cultures made from a culture or from the blood, the stab is noticeable after a day or two as a whitish line made up of closely placed dots ; in another day or two, from each dot a lot of fine whitish filaments are seen extending, often like rays from a centre. When the dots are closely placed in linear series, the white filaments projecting mostly in horizontal direction from them give to the stab a characteristic appearance, like the vane of a grey feather, the stab being the middle rib ; liquefaction has by this time set in on the surface, i.e. on the upper end of the stab, and there is here a more compact plate-like mass of filaments ; the liquefaction gradually proceeds into the depth while the surface patch of the growth increases in bulk ; the liquefied gelatine is clear, and the original surface growth occupies always the deepest part of the liquefied gelatine. When the surface patch while spreading remains adhering to the glass wall of the test tube, spore formation is observed in the threads of the bacilli, but when the growth is in the depth of the liquefied gelatine no spore formation ever takes place. After ten to fourteen days at 19–20° C. the upper half of the gelatine in the tube is quite liquefied, the liquefied gelatine is clear, and the whole growth is at the bottom of the liquefied part in the form of whitish grey fluffy masses ; when shaken the mass breaks up into whitish nebulous flocculi.

In streak culture on gelatine, the streak of inoculation is marked after twenty-four to forty-eight hours as a whitish grey line ; then a number of fine whitish threads shoot out horizontally from this line, liquefaction at the same time commencing and proceeding slowly and gradually ; the line thickens and broadens, and after a week is made up of masses of threads twisted and convoluted and forming a thick white filmy patch, which as liquefaction proceeds sinks to the bottom of the liquefied gelatine, forming here a whitish grey fluffy mass.

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[1] Esmarch some years later arrived independently at the same results.

In neutral or faintly alkaline broth kept at 36–38° C. there is, if the broth be thin, uniform slight turbidity after thirty-six to forty-eight hours: flakes small and large then appear at the bottom of the fluid, while this latter remains fairly clear. As growth proceeds, about the end of the week, there are contained at the bottom of the fluid characteristic greyish fluffy loose nebulous masses, which are masses of anthrax threads matted together: these masses increase in bulk, and extend as it were from the bottom of the fluid towards the upper parts. If during the first few days some of the flakes remain adhering to the glass at the surface of the fluid, these flakes enlarge and form on the glass, on a level with the surface of the fluid, a sort of whitish ring, somewhat like a pellicle; in this, copious spore formation takes place; but in the tubes, in which all the growth is limited to the deeper parts of the fluid, no spore formation occurs at any time, since for the formation of spores a free and copious supply of oxygen is required.

On agar mixture at 36–38° C. a thick greyish film is noticed after two days along and beyond the line of inoculation. This rapidly increases in breadth till the whole surface of the agar is covered with a sticky pasty greyish layer; this after some days shows some patches thicker than others, is light brown, and in some patches even dark brown.

On potato at 35–37° C. a thick cohesive layer like paste is formed: this is of a brownish colour, the growth is extensive after a few days. Both on nutrient agar and on potato, the film is a mass of threads matted together, and after two to three days copious spore formation is noticed in many threads; at the end of ten days to a fortnight the whole of the film is a mass of spores; little of the original bacilli is recognisable.

Whenever spores are formed in a culture (their mode of formation has been described on a former page), they remain active and living for indefinite periods, i.e. the spores when at any time sown into new suitable medium are capable of germinating and producing new crops of bacilli, and are capable of producing anthrax when introduced into an animal (mouse or guineapig) by spray or inoculation. But when no spores are developed, e.g. in gelatine and in broth tubes in the depth of the medium, and when none of the growth has remained adhering to the glass on the surface of the medium, the growth proceeds till all nutriment is used up; but before this point is reached, numerous bacilli, parts of the threads, and whole threads undergo degeneration; the protoplasm in the bacilli and threads becomes granular, and gradually disappears till only the empty sheaths—many of them collapsed—are left. This process of degeneration is noticeable in gelatine and broth already after a few days. In broth cultures in which the growth occurs in the depth of the fluid, in the form of the characteristic fluffy masses above mentioned, degeneration once set in rapidly extends to the whole mass; by this the mass diminishes in bulk and becomes more transparent (*see* the Report of the Medical Officer of the Local Government Board for 1882). From such cultures after some time—several weeks to several months—no new sub-culture can be established, and no anthrax can be produced in animals. In agar, which has strong alkaline reaction, this process of degeneration is also noticeable without spores being formed; the growth on the surface of the agar after several weeks to several months shows no longer any good anthrax threads, but is made up of granular *débris*.

The writer has described this degeneration as occurring occasionally in the bacilli while in the blood and in the spleen. It has been noticed within forty-eight hours in guineapigs and in sheep that died of typical anthrax, in which the number of the bacilli in the blood and particularly in the spleen were enormous; in well-stained and well-washed cover-glass specimens large numbers of the bacilli showed the degeneration distinctly—either the protoplasm of the whole bacillus was in a state of granular degeneration, or part of a chain was in that state (*see* fig. 60).

A change observable in the bacilli of cultures (gelatine, broth, agar, potato) and generally taken to be due to involution consists in the fact that one or the other elementary individual of a chain or thread appears swollen up, thickened, spindle-shaped, club-shaped, or even spherical. In the threads, in longer or shorter portions, all the elements may thus be changed. The writer has described and figured these changes (fig. 70) as the torula forms of bacillus anthracis; they were particularly abundant in neutral gelatine after two to three days. He has had cultures where some of the anthrax threads were thus transformed into chains of torula-like large elements—many times thicker than the typical bacilli—strung together into beaded necklace-like strings by thin short connecting bridges; there were other threads present, in which some elements were spherical, others oval; the appearances here described were exactly like those occurring in saccharomyces mycoderma. He has also shown that those torula-shaped bacilli are very virulent, and he cannot for a moment agree with the general assumption that this change always indicates involution and degeneration. We have observed this change in other bacilli, e.g. bacillus filamentosus, bacillus tuberculosis, bacillus of diphtheria, and bacillus of cholera, under conditions and at periods in which an involution and degeneration is not probable. On the contrary, we are inclined to think that these changes mean a reversion to a former type—atavism, in fact—from which the bacilli at an early phase of the life-history of the species have sprung; so that the typical bacilli, as we generally know and see them, are merely one form set in permanency, as it were, while the conditions of growth remain of a particular kind, e.g. in the animal body they always remain bacilli. But under altered conditions, e.g. in cultivations, many of the bacilli, though the single bacilli and their threads are of the typical kind, while the cultures are recent, soon revert or at any rate have a tendency to revert to the atavistic forms.

We have in the foregoing described the peculiar characters of the bacillus anthracis in microscopic specimens and in cultures; now, though they are peculiar and characteristic, they are nevertheless not exclusive, for there exist bacilli which resemble them in a marked degree, e.g. the bacillus filamentosus repeatedly mentioned; though this latter grows considerably quicker than, and is different in streak culture from, the bacillus anthracis, yet a mistake between the two is not inexcusable, owing to the similarity of the appearances presented by both in gelatine plates and in gelatine stab cultures; morphologically, i.e. under the microscope in the fresh or dried and stained specimens, they are quite indistinguishable. Hueppe also describes a bacillus obtained and isolated from earth which in morphological and cultural respects bears a very close resemblance to the bacillus anthracis; but neither the bacillus filamentosus nor the bacillus of Hueppe inoculated into animals produces anthrax. We have above mentioned certain fatal acute forms of human septicæmia in man (Bordoni Uffreduzzi) in which the proteus hominis was found in the blood and the organs. Here a mistake for anthrax is not easily made if cultures with the bacilli are instituted; but if from the pathological appearances at the *post-mortem* examination and from the presence of the bacilli in the blood and spleen alone, the diagnosis be made, a mistake, i.e. for anthrax, is also here possible. As regards animals, the cases are not at all rare where such a mistake has actually occurred, e.g. in sheep, cattle, pigs, dying under symptoms and pathological appearances resembling anthrax. Take, for instance, malignant œdema, symptomatic charbon, and possibly other diseases : the appearances at the *post-mortem* may greatly resemble those of anthrax, the bacilli resembling to a certain extent, in size and general appearance under the microscope, those of anthrax; the diagnosis by culture would, no doubt, throw great light on the nature of the bacilli, but a simple and decisive—in fact, the best and only reliable—diagnostic means is inoculation of mice or guineapigs with the blood or spleen of the questionable case. The appearances in the mouse and guineapig dead of anthrax are very characteristic, the spleen being dark and many times enlarged, the blood of the general circulation and of the spleen being crowded with the bacilli; cultures from the blood of these experimental animals and further inoculations of mice and guineapigs can now be easily made, and the diagnosis fully established. The writer remembers the death of two sheep having been brought to his notice, where it was important, for taking preventive measures, to decide at once whether or not the sheep had died of anthrax. The *post-mortem* appearances were certainly very like those of anthrax, but there were only a few bacilli found in the blood. The spleen was enlarged, but not to a very conspicuous extent: it was dark, the lungs were congested and inflamed, in the juice of the lung and spleen numerous bacilli were found, and in sections through the lungs many capillaries were almost filled with the bacilli. In stained cover-glass specimens, and in stained sections, it was extremely difficult to say the bacilli were not anthrax bacilli. The question was, however, soon settled. Several mice and several guineapigs were inoculated, each with several drops of the blood of the spleen of the sheep ; none of these animals became in the slightest degree affected. From this of course there was justification for saying that those sheep did not die of anthrax, and the diagnosis was fully confirmed by the fact that, though no preventive measures of any kind had been taken on the farm on which those two sheep had died, no further cases of illness or death occurred either amongst the sheep or cattle, of which a considerable number were kept on the farm.

In all cases of doubt as to anthrax, inoculation of mice and guineapigs, particularly the latter, with a few drops of the blood of the spleen is the quickest and surest means of diagnosis; if in these inoculated guineapigs typical anthrax with the typical bacilli (shown by cover-glass specimens and cultivation) in the blood and enlarged spleen results, then the diagnosis is clear ; if this result does not follow, no diagnosis of anthrax can be made safely.

Buchner maintained that by successive cultivation in broth he succeeded in changing the bacillus anthracis, virulent at starting, into an inactive bacillus in morphological respects identical with the motile hay bacillus ; and further that he was able by successive cultivations in certain broth cultures to change the motile hay bacillus, inactive on animals, into a non-motile bacillus, identical in morphological respects with the bacillus anthracis, and capable of producing typical anthrax in mice. These assertions have been proved to be erroneous, and Koch ('Mittheil. aus d. k. Gesundheitsamte,' I.) and the writer (Report of the Medical Officer of the Local Government Board for 1881) have shown the probable sources of these errors. All observers agree in this, that, through however many generations the bacillus anthracis be cultivated in broth, in gelatine, in serum, in agar, on potato, it always remains bacillus anthracis morphologically and physiologically. It may, owing to peculiar soil and other conditions of culture, diminish in virulence, and even lose its virulence altogether, as will be presently shown, but it nevertheless always remains morphologically the bacillus anthracis ;

but bacillus anthracis under ordinary conditions of cultivation, such as used by Buchner, does not lose its virulence.

Hueppe, as mentioned above, isolated from earth a bacillus which in morphological respects coincided with the bacillus anthracis; inoculated into mice it did not produce any disease, but, strange to say, protected the mice against inoculation with virulent anthrax. Hueppe concludes from this that his earth bacillus is real anthrax bacillus, which in course of time, and owing to its habitat and perhaps other conditions, has lost its power to produce anthrax, but nevertheless, though not apparent, has retained some kind of chemical action like anthrax. It is difficult to judge of and criticise these results; but without altogether declaring them improbable, this much can be said, that very clear evidence will have to be brought forward to support such assertions, which at present are not, it seems, forthcoming. *A priori*, it seems improbable that in the soil the true active bacillus anthracis should change into a non-active bacillus, or *vice versâ*, seeing that the bacillus anthracis can thrive well in the soil and remain virulent for generations (e.g. the countries in which anthrax is endemic and in which infection is carried out by the soil). Further it is extremely improbable that a bacillus not causing any diseased condition should be capable of protecting against virulent anthrax; and lastly there is reason to doubt whether in mice protection against virulent anthrax can be at all or at any rate so easily produced as would seem from Hueppe's assertion.

The first observations that bacillus anthracis can become attenuated in its action without losing its morphological and biological characters were recorded by Toussaint, who found that heating anthrax blood up to 55° C. for a few minutes incapacitates such blood from producing anthrax on inoculation. Chauveau then found that the same attenuation and destruction of virulence occur when the virulent bacillus anthracis, e.g. the blood, is subjected to the action of 5 per cent. carbolic acid for a few minutes. But Pasteur was the first who showed that when bacillus anthracis is cultivated in broth at a high temperature (42·5° C.) it gradually loses its full virulence, and when such cultures are inoculated into sheep and cattle a mild and transitory form of anthrax is produced; animals so treated withstand successfully the further inoculation of virulent materials: they are therefore protected by the inoculation with the attenuated cultures. Pasteur has shown by a large number of experiments carried out in France and elsewhere that, by inoculation of such attenuated cultures, protective inoculation can be effected on sheep and cattle. He used two kinds of culture, for protective inoculation: (*a*) first vaccine: this is a culture of anthrax bacillus in chicken broth kept at 42·5° C. for fourteen days; when inoculated into sheep or cattle it produces only a slight local tumour. After about twelve days the animals are inoculated with (*b*) second vaccine: this is chicken broth culture kept at 42·5° C. for a week only. This culture produces also a local effect with slight constitutional disturbance, more pronounced than after the inoculation of the first vaccine; but the disturbance is only transitory and the animals recover. Up to nine months, such animals are refractory against inoculation with virulent anthrax blood.

If the second vaccine is used for the primary inoculation, the effect is more severe, and may lead to fatal general anthrax; this second vaccine having been grown for one week only at 42·5° C. is therefore stronger, and is of a higher degree of virulence than the first vaccine, which had been grown at the high temperature for a fortnight. Though theoretically correct, and fully confirmed by numerous experiments, there are several difficulties in the way of the practical application of this protective inoculation: (1) Since it is a question of making such vaccine on a large scale—and this must be of course the case if it be used in practice, e.g. for whole flocks of sheep and herds of cattle—the exact method and way of getting the right degree of virulence is not easily achieved. Some years ago (1882, 1883) the writer bought some Pasteur's vaccine made in Pasteur's laboratory, and sold in tubes by Pasteur's agent, M. Boutroux, and it was used on guineapigs and sheep. Of the guineapigs inoculated with first vaccine a certain percentage died of typical anthrax; with second vaccine the percentage of death was greater. Of the sheep that had been inoculated exactly after Pasteur's prescribed method, one of four died with anthrax from the second inoculation, i.e. with second vaccine; of five sheep treated with the two Pasteur's vaccines, and afterwards subjected to inoculation with virulent anthrax blood, one died after two days, a second one after a week, and three proved refractory, i.e. were protected. Such or similar results were recorded also by other experimenters. (2) The vaccine manufactured thus by Pasteur on a large scale is not always pure anthrax; there are present other organisms besides anthrax bacilli. Vaccine thus contaminated may therefore harbour bacilli—e.g. those of malignant œdema—which are not desired, since these themselves may produce in sheep and cattle undesired results. But it ought to be in fairness stated that the published statistics on the greatly decreased mortality amongst sheep and cattle, since Pasteur's protective inoculations have been used in the localities in which great devastations by endemic anthrax (France, Russia) had previously occurred, bear out Pasteur's contention as to the practical use of the protective inoculation with his anthrax vaccine. (3) A third serious difficulty is this: Koch and Gaffky have shown that animals (sheep) protected by Pasteur's vaccines against further *inoculation* with virulent anthrax prove unprotected, or almost wholly so, if they are infected with spores by feeding; for by this method Koch and Gaffky have shown that such sheep become infected with typical anthrax; and it is precisely this method of infection, viz. by spores taken in by the alimentary canal, that obtains amongst sheep and cattle under natural conditions, as has been mentioned on a former page. Other modes of protective inoculation have been recorded by Perroncito, Kitt, and others. The writer has shown (Report of the Medical Officer of the Local Government Board, 1882) that mouse's anthrax blood is attenuated anthrax, and can be used for protective inoculation of sheep; guineapig's anthrax blood mixed for a few minutes with a large quantity of solution of perchloride of mercury, of the strength of 1 : 25,000, is sufficiently attenuated for sheep (*ibid.* 1885). It produces a slight illness and protects against further inoculation with virulent material.

Wooldridge ('Proc. Royal Society,' 1887) has shown that in cultures of bacillus anthracis—in a particular alkaline albumen—chemical substances are present which have a powerful protective influence, inasmuch as when injected into the vascular system of rabbits they provide at once protection against inoculation with virulent anthrax. Hankin then showed that in certain proteid material the bacilli anthracis produced a poisonous albumose, to which the pathogenic action of the bacilli is due; and Sidney Martin further proved that these albumoses give further origin to a 'poisonous alkaloid,' which he isolated, and obtained as a salt in a crystalline form.

The writer has shown that anthrax bacilli, derived from virulent disease (blood of a guineapig dead of typical anthrax), when grown in gelatine medicated by the admixture of perchloride of mercury, 1 : 40,000, suffer an attenuation of their virulence; though the growth is apparently normal, and when transferred to new normal nutrient gelatine yields normal typical anthrax growth: nevertheless it either does not produce death at all, or only after many days.

This mode of producing attenuated anthrax depends, however, to a large extent on the primary degree of virulence of the bacilli at starting. While anthrax bacilli which possessed at starting a high degree of virulence suffer slight attenuation by this method, others not of a high degree of virulence at starting are easily attenuated in their virulence by this method (*see* Reports to the Medical Officer of the Local Government Board, 1885–86).

While sheep, cattle, and rabbits that have once passed through a mild form of anthrax are, as a rule, refractory against further inoculation with virulent anthrax, this is not the case with some other animals, for instance, guinea-pigs. Of these the writer has shown that only in a very small percentage (less than 4 per cent.) can a real protective inoculation be effected; the rest, though sometimes protected against one, two, or even three successive inoculations with less virulent anthrax, eventually succumb to virulent degrees of anthrax (Report of the Medical Officer of the Local Government Board for 1887, p. 291).

As mentioned in a former chapter, Ogata and Jasuhara have shown that a previous or simultaneous injection of the blood of an insusceptible animal (rat, dog) protects from, and neutralises the action of virulent anthrax in mice. Hankin obtained a glycerine extract from the spleen of a rat, which also protected mice against anthrax. Normal frogs and rats, insusceptible to anthrax, become susceptible to it if previous to, or simultaneous with, or immediately after, inoculation with anthrax blood or anthrax culture (spores or bacilli) they are subjected to narcosis with ether-chloroform.

The fact that frogs kept at the temperature of a warm-blooded animal are hereby rendered susceptible to anthrax (Petruschki) has been mentioned in a former chapter.

The disease of silkworms known as *pébrine*, and showing itself in minute grey or black patches all over the body of the silkworms, has been shown experimentally to be contagious, and generally communicated to the worms by food (mulberry leaves) which had been previously tainted with the contagium. This latter, known as 'Cornalia corpuscles,' first discovered by Cornalia, is composed of oval microscopic corpuscles which by some are declared to be oval cocci, hence also termed micrococcus ovatus; Lebert, Naegeli, and others have shown them to be the living contagium of the disease. These corpuscles enter by the alimentary canal of the worms, multiply there enormously, and spread thence into all the tissues; they are transmitted by the moth to the eggs, multiplying within the body of the chrysalis, and reaching their maximum development in the worm, in which the disease declares itself as *pébrine*. Pasteur has shown experimentally that the time at which the silkworm, during its existence as worm, becomes infected has a very important bearing on the period at which the disease shows itself in the worm, moth, or chrysalis respectively.

The Cornalia corpuscles, also called nosema bombycis, are by some observers, amongst them Naegeli, declared to be a form of bacteria; others, like Pasteur, Balbiani, and Leydig, declare them to be psorospermiæ. Pfeiffer has studied them carefully and extensively, and has shown that they are a species of sporozoa (*see* his paper in 'Zeitschr. f. Hygiene, III., p. 469).

Another infectious fatal disorder of silkworms is the one known as *flacherie*: it is not associated with the cutaneous spots of the *pébrine*, but the worms affected with the disease show a typical limpness and relaxation, become very weak, and ultimately die. The corpuscles that are present in the worms, and believed to be the cause of the disease, are called microzyma bombycis of Béchamp; they are oval cocci, forming longer or shorter chains; hence are also called streptococcus bombycis. They have been found by Cohn in enormous numbers in the intestinal canal of the affected worms. By mixing with the mulberry leaves the intestinal contents of affected worms, and feeding thereon healthy worms, these latter contract the disease, and their alimentary canal, previously free of the streptococci, becomes now full of them.

Foulbrood of Bees.—A fatal infectious disease of bees has been investigated by F. R.

Cheshire and Watson Cheyne, and has been shown by the latter to be caused by a slightly motile bacillus, the *bacillus alvei*. The single bacilli measure 2·5–5 μ in length, 0·8 μ in thickness, forming in cultures longer or shorter threads, and in these oval spores, 2 μ long, 1 μ thick, make their appearance. The growth of the bacilli in gelatine plate cultivations is very characteristic: in their first appearance the colonies are round or oval discs, next they become pea-shaped, and more or less drawn out at one or more points into longer or shorter processes: these become branched. Under the microscope the branches are straight or circular, or possess irregular thickenings; the same projections are seen to arise in the streak cultures as well as stab cultures in gelatine; the branches, projections, and filamentous processes are seen under the microscope to be bundles of bacillary chains or filaments. That this bacillus is really the cause of the fatal disease has been proved experimentally by Cheshire and Watson Cheyne by feeding healthy bees with spores, or bacilli and spores, of the artificial cultures. ('Journal of the Royal Micr. Soc.' March 1885.)

CHAPTER XVI

EPIDEMIC PNEUMONIA—INFLUENZA

By the researches of Leyden and others it has been shown that the disease known as lobar or croupous or fibrinous pneumonia belongs to the group of infectious diseases. It has this in common with infectious diseases, that it occurs simultaneously in a number of persons living under the same conditions of place and surroundings; that it runs a definite course; that its symptoms and pathology are the same or very much alike in all cases; and last, but not least, that in several instances the disease has been communicated within the same household from one person to another. Only during recent years has bacteriological investigation shown that not all acute croupous pneumoniæ are of exactly the same kind. Though in all there is the viscid gelatinous sputum, more or less rusty or prune-juice-coloured during the first three or four or five days, giving way to a less viscid, more greyish, more purulent expectoration, and though in all of them there is an early or red solidification or hepatisation, leading gradually to a more grey infiltration (grey hepatisation) of one or more lobes of one or both lungs, associated with more or less extensive pleuritis: yet there are certain differences of detail which seem to show that croupous or epidemic pneumonia is a name which ought to designate more than one species of acute infectious pneumonia.

In the genuine croupous pneumonia, the lobar fibrinous pneumonia generally involves but one lung; the sputum is, as is well known, of a characteristic gelatinous consistency; it cannot be poured out of a vessel, since it forms a very tenacious viscid material; it is of a gelatinous transparency, contains a number of air bubbles, and in the early stages is scanty. During the first few days (three to five days) it is streaked with rusty or reddish streaks and patches, which colour is due to the presence of red blood-corpuscles; the sputum is transparent and contains under the microscope red blood-corpuscles, a few leucocytes and swollen alveolar epithelial cells; fibrin threads are seen to permeate the whole. This condition is, however, only observed during the first few days; after the fifth or sixth day the sputum becomes more copious, less rusty, and more grey; under the microscope few red blood-corpuscles, but crowds of leucocytes, are seen and few threads of fibrin; and when the disease has passed its height (sixth to ninth day) the sputum becomes semi-fluid and greyish white, and under the microscope appears almost uniformly made up of leucocytes.

On *post-mortem* examination of cases dying during the first four or five days, the most prominent symptom is the pneumonia; generally one lung, rarely both, shows in one or more lobes well-marked-off intense inflammation, the tissue being in a solid state, intensely congested, dark purple red—red hepatisation. When an incision is made, copious almost fluid blood oozes out of the cut surface; pieces of such a lobe sink in water. The pleura is opaque and injected, and its cavity contains in some cases more, in others less, sanguineous serous exudation: the right heart contains clotted blood. In cases that die after the seventh to ninth or tenth day the inflamed lobes are less red than in the former stages, but solid, and portions of them sink in water; on incision the surface is less juicy, is grey—grey hepatisation. Congestion of the liver, spleen, and the cortex of the kidney, and inflammation of the pleura and pericardium, with serous and fibrinous exudation are occasionally present, particularly of the pleura, which latter condition is generally observed at the *post-mortem* of early cases, i.e. those that die in the stage of red hepatisation. Ecchymoses into the mucous membrane of the stomach and intestine are sometimes observed in such cases.

On microscopic examination of the red hepatised lung, one finds all the blood-vessels of the inflamed lobes intensely congested, the blood-vessels, including the capillaries around the air cells, engorged with blood; the alveolar cavities, infundibula, and minute bronchi are distended by, and filled with a dense network of fibrin threads, in whose meshes are situated numerous red blood-corpuscles and a few leucocytes, isolated or in groups; the epithelial cells lining the alveoli are swollen and detached from the wall, and are contained within the fibrinous mass. The substance of these epithelial cells is granular and contains vacuoles; in the alveolar wall, and in the peribronchial and interlobar connective tissue, blood is present *en masse*. Around the branches of the pulmonary artery, and around the small and large bronchi, are found numerous leucocytes. In the stage of grey hepatisation the air cells and infundibula and small bronchi are filled with a network of fibrin, and in their meshes very numerous leucocytes, a few red blood-corpuscles, and a few epithelial cells are discernible; in this stage leucocytes are found also in the alveolar walls and in the peribronchial tissue (figs. 33 and 34). Examined under the microscope the liver appears congested; the liver cells are slightly swollen and granular, and in most lobules many of the cells contain fat globules, i.e. show fatty degeneration.

In the kidney the epithelium of the convoluted uriniferous tubules shows opaque swelling and granular degeneration.

The first statements that a definite microbe is present in the sputum and in the exudation, contained in the air cells, were made by Friedländer. Though Klebs, Koch, and others had previously described cocci as occurring in the exudation, Friedländer[1] and Frobenius first demonstrated by the culture test the presence of a definite species of *capsulated oval cocci*, called by them pneumococci, but now known as the *bacillus of Friedländer*, since it has been shown that the coccus is only a phase in the growth and multiplication of the microbe, and that this is really a rod-shaped organism, a bacillus. It occurs as oval cocci, as single rods, as chains of oval cocci or rods. In the sputum and in the exudation of the lung it is characterised by a hyaline capsule, each coccus or rod when isolated being surrounded by it, or it forms a common capsule round a dumb-bell of the oval or rod-shaped elements; in cover-glass specimens of the sputum or lung exudation the capsules can be stained in a different colour from the rods, either by over-staining the whole, e.g. with carbol-methyl blue or Weigert's gentian violet, and then well washing with spirit. By this means the capsule remains faintly stained while the cocci or rods retain a deep colour : or by Gramm's method—first stain in gentian violet, then in eosin ; or by double staining first with methyl blue or gentian violet and then with eosin. In sections through the hardened lung, the capsulated rods and cocci can be shown by well staining with carbol fuchsin (half to two hours), then washing in alcohol for some time (half to one hour).

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[1] *Fort. d. Med.* vol. i. 1883, No. 22.

This bacillus of Friedländer, when it occurs, appears in the stage of red hepatisation, and disappears during the further stage. It shows the following characters in cultivation, whether derived from the sputum or the lung juice: in stab cultures in nutritive gelatine it forms a whitish line, which gradually thickens, and which, on the surface of the stab, forms a convex, rounded, greyish, or greyish-pink knob, the culture thus resembling a 'nail,' in which the linear growth in the stab is the nail pin, the convex knob at the upper end of the stab the nail head. In plate cultivation it forms small round greyish-white colonies, those situated on the surface of the gelatine being convex. The bacilli and cocci of the cultures have no distinct capsules.

Friedländer and Frobenius and other observers afterwards tried to show the pathogenic action of this microbe on rodents—mice and guineapigs. They did not succeed in producing any pathogenic action by injecting the cultures subcutaneously, but on inoculation into the pleural cavity and the lung tissue (by means of a Pravaz syringe, the cannula of which pierces the wall of the chest) those observers produced definite results: pleuritis and pneumonia, and in the pleural exudation and inflamed lung the capsulated bacilli were found in great numbers. The writer has in 1883 (*see* Report of the Medical Officer of the Local Government Board for 1884) shown that by subcutaneous injection of sputum of croupous pneumonia (from the stage of red hepatisation) into rabbits and mice, acute septicæmia is sometimes produced ; in the blood, pleural and pericardial exudation, and in the congested lung of such animals the capsulated bacillus of Friedländer can be demonstrated in large numbers. The writer has in that paper taken exception to the assumption made by Friedländer as to the true pathogenic nature of the so-called pneumococcus of Friedländer ; that is to say, from the inconstancy, scarcity, and unequal distribution in the human lung of this microbe, and owing to the septicæmic action on mice and guineapigs, and to the method of experimentation used by Friedländer and others in order to demonstrate that this microbe is the true pneumonia microbe, the writer has differed from the proposition that the bacillus of Friedländer is the microbe of croupous pneumonia. Passet has shown that a capsulated microbe in every respect identical with Friedländer's pneumonia bacillus occurs elsewhere and independently of croupous pneumonia—is, in fact, probably a normal inhabitant of the fluid of the mouth and throat, and is present in the normal sputum. A. Fränkel,[1] and independently at the same time Weichselbaum,[2] have by a very large series of observations, made on very numerous cases of genuine lobar or croupous pneumonia in the stage of red hepatisation, shown that the bacillus of Friedländer occurs only in a small percentage of cases; but that almost invariably there is present in large numbers, both in the sputum and the lung juice, an oval capsulated coccus, and they justly conclude that Friedländer's bacillus cannot be causally connected with pneumonia.

The coccus which Fränkel and Weichselbaum independently discovered is capsulated, and occurs as a rule as a diplococcus ; occasionally the diplococcus is arranged in shorter or longer chains. This diplococcus does not grow on gelatine at 20° C.; it requires higher temperature, at least 22° to 24° C., i.e. it cannot grow at ordinary temperature, but nutrient agar or blood serum has to be employed. In agar plates or serum plates it forms rounded white colonies; on the surface of the agar or serum, in streak culture, it grows as a whitish film; on potato the growth is thin and white, dry and difficult to see. Recent cultures of the microbe inoculated subcutaneously, or better still into the peritoneal cavity, produce in rabbits and mice a general septicæmic infection; cultures carried on for several generations gradually lose all virulence. Owing to the fact that this diplococcus pneumoniæ of Fränkel and Weichselbaum has been found by them and by others as a constant and numerous inhabitant of the sputum and lung juice of true croupous pneumonia in the acute stage, it is considered as the real microbe of this pneumonia. These facts have hitherto been confirmed by a large number of independent observers.

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[1] *Deutsche med. Wochenschrift*, 1885, No. 31.

[2] *Wiener med. Jahrbücher*, 1886, p. 483.

Notwithstanding the very extended observations of Fränkel, Weichselbaum, and of many others in relation to the diplococcus pneumoniæ and its distribution, it is perfectly justifiable to question whether this is the microbe of all cases of croupous pneumonia, and whether it is the only essential etiological factor in the croupous pneumonia. Croupous pneumonia is in its pathology and clinical aspects a well-defined disease, and it is curious to find that the identical microbe should also be the cause of such widely different diseases as acute purulent otitis, cerebro-spinal meningitis, and acute peritonitis (*see* below). Further, Weichselbaum ('Wiener med. Blätter,' XIII., No. 6), examining the sputum derived from twenty-one patients affected with bronchitis after influenza, found the diplococcus pneumoniæ constantly present in considerable numbers, yet only in two or three cases did croupous pneumonia actually supervene; again, Besser (Ziegler's 'Beiträge zur path. Anat.,' Band VI., 4) found in the normal secretion of the nasal cavity in fourteen out of eighty-one cases, the presence of the diplococcus pneumoniæ in many instances so numerously as to form a pure culture. He further met with the diplococcus pneumoniæ in the bronchial mucus of cases of fracture of cervical vertebræ, in one case of tuberculosis of the peritoneum and in one of enteric fever; and lastly Neumann ('Centralb. für Bacteriologie und Parasit.,' VII., No. 6) points out that the micrococcus pyogenes tenuis of Rosenbach, which has been described by Rosenbach and others in connection with various kinds of purulent processes (empyema, abscess on the neck, on the leg, and in the processus mastoideus, &c.), and considered to be one of the species of microbes capable of causing suppurative changes, is identical with the diplococcus pneumoniæ. All these facts would point to the conclusion that a particular condition of the lung is essential for the diplococcus to cause the pneumonia.

Finkler in an exhaustive treatise on Acute Pneumonia ('Die acuten Lungenentzündungen als Infections-Krankheiten,' Wiesbaden, 1891), summarises, p. 286, his own observations and those of others thus: (1) Fibrinous pneumonias are caused particularly by the diplococcus pneumoniæ; (2) broncho-pneumonias are bacteriologically not a single disease; (3) cellular pneumonias are caused chiefly by streptococci.

There have occurred cases of pneumonia in batches and in epidemics in which a direct infection from person to person has been demonstrated, pneumonias which in many respects resemble the ordinary croupous pneumonia: the symptoms are similar and the course is only slightly different; the sputum is of the same viscous consistency but less prune-juice-coloured, more grey; in the later stages the sputum is whitish grey and more fluid.

Under the microscope few red blood-corpuscles, but numerous leucocytes, are seen in the early stages, but otherwise the sputum looks very much the same as in the above croupous pneumonia; in the later stages it is also crowded with leucocytes. The lung shows also a stage of red and a stage of grey hepatisation, the latter gradually following the former. The naked eye appearances of the lung differ very little from the true croupous pneumonia, except that the demarcation of the inflamed lobes from those not inflamed is not marked, that the pneumonia is generally double-sided, and that the lung is more flaccid; sections of the lung in the stage of red hepatisation examined under the microscope show only a few red blood-corpuscles in the exudation of the air cells, but very numerous leucocytes and a few detached epithelial cells in a network of fibrin. In this respect there exists a difference between this kind and the true croupous pneumonia in the stage of red hepatisation; in the latter the network of fibrin is more copious, it contains few leucocytes and chiefly red blood-corpuscles; whereas in the pneumonia under consideration, even in the earliest stages, the alveolar cavities already contain numerous leucocytes—in fact, appear crowded with them. Now in these pneumonias neither the bacillus of Friedländer nor the diplococcus of Fränkel and Weichselbaum can be demonstrated. The cases of infective pneumonias of this kind that the writer has seen were those investigated by Dr. Ballard in Middlesbrough, and described by him in the Report of the Medical Officer of the Local Government Board, 1889. The pathology and clinical history of these cases have been described by Dr. Ballard, and on comparing them with what is known of the ordinary croupous pneumonia, there are only slight differences to be noticed.

Cover-glass specimens made from the sputum or the bloody juice of the lung show bacilli in large numbers; they are neither Friedländer's nor are they the capsulated diplococcus of Fränkel-Weichselbaum occurring in genuine croupous pneumonia; these bacilli are present in the juice of the inflamed lungs in pure culture. They are short, oval rods, some are constricted in the centre, they occur singly or more commonly as dumb-bells, or also, but rarely, as short chains, but there are always rods amongst them which are longer and more cylindrical. Cultivations made on the surface of nutrient gelatine (in plate or in test tubes) with such lung juice bring forth pure cultures of the microbe; and it is hereby seen by the large number of colonies that come up, if even only a trace of the lung juice be used, that those bacilli must be present in the lung in very large numbers. In preparations made of such colonies many of the microbes are short and oval rods, but there are now a good many longer bacilli visible, and after several days' growth even long filaments made up of cylindrical bacilli can be found. The size of the bacilli prepared from the sputum or the lung juice or from cultures is this: the thickness 0·3 to 0·4 μ, length 0·8 to 1·6 μ and more. The bacilli in the fresh state are motile, though these are only few in number; a good many individuals do not show it. In cultivations the motile forms occur only if the culture is on the surface, e.g. on gelatine, on agar, or potato, and in these only while the culture is of recent date; in broth after two days' growth at 37° C. motile forms are missed. The motility consists in the bacilli darting through the field of the microscope or spinning round very rapidly. These facts as to the bacilli showing motility only when growing on the surface of the nutrient medium show that a free supply of oxygen is required to maintain such motility. But the great requirement of oxygen during the growth and multiplication of the bacilli, i.e. that they are aërobic, is also shown by the fact that they do not grow well and rapidly in the depth, though they grow and multiply with enormous rapidity on the surface of the nutritive media. When growing in a gelatine plate cultivation, those colonies that develop on the surface grow incomparably faster than those which develop in the depth; while the former in a few days reach the breadth of several millimetres, the latter at the same distance of time are only minute points. The colonies when first appearing (twenty-four to forty-eight hours) on the gelatine are minute grey round dots; soon they spread out into translucent plaques, of which the margin is thinner than the centre, being at the same time irregularly crenated; under a glass the colonies are uniform and light brownish in colour. In about ten to fourteen days the diameter of the plaques reaches as much as half an inch. The nutrient gelatine does not become liquefied at any time. In streak culture on gelatine the streak is already after two to three days occupied by a translucent greyish white band, 2–3 mm. wide, thicker in the middle than in the margin, which latter is very irregular and crenate. In the stab culture in gelatine the stab becomes indicated by a thin grey line made up of minute grey droplets, the size of which always remains small, whereas on the upper or free end of the stab there is present a thin greyish translucent patch, rapidly expanding and of irregular and crenate outline. On agar mixture at 36–37° C. the growth forms in a few days a thin whitish-brown pasty pellicle; in alkaline broth at 37° C. the bacilli grow very rapidly, after twenty-four hours producing strong turbidity, after two to three days yielding a whitish floccular sediment; no real pellicle is formed on the surface of the broth. On potato at 37° C. the growth after a few days is a light brown-coloured, pasty, moist layer.

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The cultures as also the lung juice act virulently on mice and guineapigs, on the former more than on the latter. Subcutaneous inoculation produces disease and death in the course of thirty to 100 hours. On *post-mortem* examination both lungs are found intensely inflamed, some portions in a state of red hepatisation; generally there is present pleurisy and pericarditis and peritonitis, with more or less sanguineous exudation. The spleen is enlarged in mice, but not in guineapigs. The bacilli can be easily demonstrated in very large numbers both by cover-glass specimens and by cultures in the heart's blood, the lung juice, and the spleen of the mice, and in the lung juice of the guineapigs.

The lung juice, or cultures derived from the tissues of the infected mice or guineapigs, inoculated into further mice or guineapigs, produce the same disease and death with the symptoms just described.

While working with cultures of these bacilli on mice and guineapigs there occurred amongst normal mice and guineapigs, kept in the same stalls as the experimental animals, an epidemic of pneumonias, leading to death of a great many of them; on *post-mortem* examination all showed exactly the same appearances as the above experimental mice and guineapigs, and the juice of the inflamed lungs contained the same bacilli in crowds.

Three monkeys, kept on the same premises and which most probably became accidentally infected by food, died of pneumonia. In the inflamed lungs the bacilli could be easily demonstrated by cover-glass specimens and by culture.

It may be added here that in two out of five cases of croupous pneumonia following after influenza, the writer has found the same bacillus in large numbers, almost in pure culture; its cultural characters and its pathogenic action on mice were the same as in the Middlesbrough cases.

Amongst a number of pneumonias not connected with influenza, the same bacillus has been demonstrated in a small percentage of the cases, but in these the bacilli were present in pure culture.

Foà ('Deutsche mediz. Wochenschrift,' 1889, No. 2) describes cases of croupous pneumonia which were neither associated with the bacillus of Friedländer nor with the diplococcus of Fränkel-Weichselbaum. In the sputum, in the fluid withdrawn from the inflamed lung during life by means of a syringe, and in the hepatised lung after death, he met with a micrococcus, which, owing to its shape and being capsulated, he called micrococcus lanceolatus capsulatus. This by its morphological and biological characters was recognised as a definite and separate species. Cultures of it in broth could easily be made, also on agar and on blood serum; it did not grow on potato or on gelatine. On mice, guineapigs, and rabbits it acts virulently, on the latter always if inoculated in large quantities; the animals dying in two to three days. Injected into the peritoneal cavity, it produces peritonitis with serous fibrinous exudation; subcutaneously, it either produces rapid septicæmia and death, or a severe local œdema and death.

Mosler ('Deutsche mediz. Wochenschrift,' 1889, Nos. 13 and 14) describes cases of croupous pneumonia occurring in one family, and clearly communicated directly from one member to the other. On *post-mortem* examination both lungs were found affected with fibrinous pneumonia, the character of the hepatisation being of a hæmorrhagic kind, and there was also hæmorrhagic fibrinous pleuritis. No pneumococci could be found in the sputum or lung. Löffler examined the lung fluid withdrawn by a Pravaz syringe from the living patient, and in it he found very numerous examples of bacteria, belonging to one single species of bacilli which differed from Friedländer's bacillus, and from Fränkel's and Weichselbaum's diplococcus pneumoniæ. From the description of the characters in cover-glass specimens, and on agar and gelatine, the writer finds a very great resemblance to the bacilli described by himself of the Middlesbrough croupous pneumonia. However, no motility of the bacilli was noticed; but this need not surprise, since striking motility of the Middlesbrough bacillus is noticed only in recent cultures; after two to three or more days the bacilli do not show any conspicuous motility. Mosler did not succeed in producing any disease in mice, guineapigs, or rabbits, nor were the bacilli found in the lung at the *post-mortem* examination.

Various acute inflammatory diseases are associated with, and ascribed to the diplococcus pneumoniæ of Fränkel and Weichselbaum. Weichselbaum describes ('Wiener klin. Wochenschrift,' 1888, Nos. 28–32) several cases of acute meningitis: three cases of cerebro-spinal meningitis pure, one case of acute internal hydrocephalus and spinal meningitis, one case of acute encephalitis and circumscribed cerebro-spinal meningitis, one case of pneumonia of long standing, there being present at the same time ulcerative endocarditis of the aortic valves, embolism of the right arteria fossæ sylvii, and circumscribed meningo-encephalitis. In all these cases the diplococcus pneumoniæ could be demonstrated in the exudation by cover-glass specimens and cultures. In the cases of primary cerebro-spinal meningitis and meningo-encephalitis Weichselbaum constantly found exudations in the tympanic cavity and the secondary nasal cavities, and in four such cases he found in the exudations of the tympanic cavities, maxillary cavity, and the ethmoidal labyrinth an inflammatory exudation which contained the diplococcus pneumoniæ. From this Weichselbaum concludes as probable that this microbe has found its entrance into the cranium from those cavities and set up the meningitis. Weichselbaum found also, at the *post-mortem* examination of cases of croupous pneumonia, exudations in the tympanic and secondary cavities of the nose, and of the ethmoidal labyrinth, which contained the diplococcus pneumoniæ; in one case of croupous pneumonia, dead on the eighth day, he found that microbe even in the cavity of the sphenoid bone. In one case of primary pleurisy with slight pericarditis and puerperal endometritis, the diplococcus pneumoniæ could be demonstrated in the pleural, pericardial, and uterine exudations. Banti (*ibid.*) describes cases of pericarditis, and also of pleuritis, associated with the diplococcus pneumoniæ.

Foà and Bordoni Uffreduzzi likewise describe cases of epidemic cerebro-spinal meningitis associated with the diplococcus pneumoniæ ('Zeitschr. f. Hygiene,' IV., 1, p. 67).

Bonone ('Centralbl. f. Bact. und Parasit.,' IV., No. 11, p. 321) describes a case of pleuro-pericarditis and cerebro-spinal meningitis in which he found, and from which he cultivated (from the fibrinous exudation of these membranes), a microbe which, though in many respects resembling the diplococcus pneumoniæ, was, nevertheless, found to offer slight differences; for this reason Bonone calls it the pseudo-diplococcus pneumoniæ.

Weichselbaum has further observed ('Centralbl. für Bact. und Parasit.,' 1888, Band V., No. 2) cases of primary acute peritonitis, followed by pleurisy, in the exudation of which the diplococcus pneumoniæ was found in large numbers.

The same author ('Monatsschrift f. Ohrenheilk.,' 1888, Nos. 8, 9) describes a case of acute rhinitis and otitis media, followed by pneumonia of one lobe of the left lung and acute parenchymatous nephritis; in the exudation of the nasal cavity and in the pus of the tympanic cavity and mastoid cells, the bacillus of Friedländer was present in large numbers.

Levy and Schrader ('Archiv f. exper. Path. und Pharm.,' XXVI., 1889, and 'Centralb. f. Bact. und Parasit.,' VII., No. 3, p. 98) found amongst ten cases of otitis media thrice the diplococcus pneumoniæ, thrice staphylococcus pyogenes albus, once streptococcus pyogenes, once diplococcus pneumoniæ and streptococcus pyogenes, once diplococcus pneumoniæ and staphylococcus albus, and once staphylococcus pyogenes albus and cereus albus.

Zaufal, on the other hand, mentions cases of genuine acute otitis media caused by the diplococcus pneumoniæ ('Centralb. f. Bact. und Parasit.,' Band V., p. 617). Kanthack ('Zeitschr. f. Ohrenheilk.,' XXI., 1890, p. 44) found in the exudation of seven cases of otitis media the staphylococcus pyogenes albus, the bacillus saprogenes of Rosenbach, and the diplococcus pneumoniæ.

INFLUENZA

Maximilian Jolles ('Wiener med. Blätter,' 1890, XIII., No. 4) asserts the constant presence of the capsulated bacillus of Friedländer in the sputum of persons who had passed through influenza, and is inclined to ascribe to it an etiological importance; but for this there is not sufficient ground, since this bacillus is present also in normal sputum, and further the pneumonia following influenza is sometimes of the character of a complication or secondary infection. With this accord Weichselbaum's observations (*ibid.* 1890, No. 6), who found in cases of pneumonia following influenza the diplococcus pneumoniæ; but he found this same microbe abundantly in the sputum of other cases of influenza, twenty-one in all, though only in two of them croupous pneumonia supervened. Weichselbaum arrives at the conclusion that the diplococcus pneumoniæ is not the microbe of influenza.

Ribbert and Finkler describe the streptococcus pyogenes as the cause of the pneumonia following influenza, and the first-named author thinks that microbe also the microbe of the influenza itself.

Professor Klebs, of Zürich ('Centralbl. für Bact. und Parasit.,' VII., 5) maintains that during the febrile stage in influenza the blood contains, 'in very large numbers, flagellate protozoa,' either free in the plasma, or adhering to or contained within the red blood discs. More recently Pfeiffer

('Deutsche med. Woch.' No. 2, 1892) described the constant presence in the bronchial sputum and in the pulmonary exudation in all cases of influenza, mild or severe, of minute bacilli, about half the length but the same thickness as the bacilli of mouse septicæmia; in stained specimens the bacilli show a characteristic bipolar granule with intermediate clear part, hence resemble a diplococcus. They are aggregated in smaller or larger clumps, occur in the leucocytes of the sputum, and also form short chains, which in stained specimens resemble streptococci. These bacilli disappear with the cessation of the disease. Kitisato (*ibid.*) cultivated the bacilli; they grow in a characteristic manner in broth and agar kept at 37° C. The broth remains clear, while a growth at the bottom of the fluid appears as whitish grey granules, and fluffy nebulous masses. On agar the growth forms minute translucent droplets which have no tendency to coalesce; the bacilli do not grow on nutrient gelatine kept at 20° to 22° C. In broth and in agar the bacilli form long threads (*see* fig. 6). Pfeiffer did not meet with the bacilli in any but influenza cases; Kitisato did not succeed in cultivating the bacilli from any but influenza sputum; Canon (*ibid.*) asserted the presence of bacilli, supposed to be morphologically the same as the above, in the blood of all cases of influenza, their number varying in cover-glass specimens between 5 and 20, occurring singly and in small groups. The writer had the opportunity of confirming Pfeiffer's and Kitisato's discovery as to the presence of the bacilli in the bronchial sputum of cases of influenza, as also, to a limited degree, the assertion of Canon as to the presence of certain bacilli in the blood ('Br. Med. Journal,' January 23, 1892). From an extensive series of observations carried out during February, March, and April, 1892, the writer has convinced himself that while Pfeiffer and Kitisato's assertions are correct, those of Canon cannot be upheld, since in over fifty cases of true uncomplicated influenza, in which the blood was examined (prolonged staining of cover-glass specimens after Canon's method with a mixture of eosin and methyl blue), in only two cases were bacilli present in appreciable numbers (*see* fig. 95), in a third case there were present but very few, and in the rest no microbes could be detected. Cultivations of the blood yielded, except in one case, no organisms. The bacilli present in the blood of the above three cases appeared larger than the influenza bacilli of the bronchial sputum.

Important observations on the different species of bacteria found in influenza are recorded by Babes, 'Centralbl. f. Bact. und Parasit.,' IX.; Friedrich, 'Arbeiten aus dem Kais. Gesundheitsamte,' VI., 2; Kirchner, 'Zeitschrift f. Hygiene,' IX., 3, p. 528; Bein, 'Centralbl. f. Bact. und Parasit.,' IX., No. 5; Fränkel, Fraser, Kartulis, and others, *ibid.*

As to pleuro-pneumonia of cattle, various species of microbes have been described as the cause of it, but none can be said to have been at all satisfactorily proved to be so (*see* the assertions of Lustig, Poels, and Nolen).

CHAPTER XVII

GONORRHŒA

In this acute infection, be it of the conjunctiva, or of the urethra, or vagina, the inflammation is essentially of the character of a severe catarrh: the mucous membrane is congested, and its tissue is infiltrated with leucocytes; these migrate into the epithelium of the surface, and through this on to the free surface. The lines occupied by the cement substance of the epithelial cells are at first the paths through which the leucocytes and exudation pass towards the surface; as these, with the progress of the disease, increase in number, they burrow also into the substance of the epithelial cells, numerous epithelial cells at the same time becoming swollen and detached. In the earlier stages the exudation passing from the surface of the mucous membrane is thin and more of a serous or thin purulent character; later on it becomes more of the character of thick pus. In the former we find numerous free epithelial cells and leucocytes; some of these epithelial cells contain vacuoles, and in them one or more leucocytes; occasionally one meets with a large epithelial cell containing in a cavity a number of leucocytes, the protoplasm of the epithelial cell being reduced to the periphery and including the compressed oval nucleus. Such epithelial cells with vesicles in which one or more leucocytes are contained, have been occasionally interpreted as epithelial cells in which pus cells are being formed by endogenous formation; but in sections through the epithelium it is clearly seen that leucocytes everywhere pass from the mucosa into the epithelium, and here they invade the epithelial cells themselves. In the later stages, when the exudation is of thicker consistency, the relative number of epithelial cells in the exudation is not so great as at first, but the number of pus cells is very great, and, indeed, causes the consistency of the exudation. Neisser was the first who pointed out the constant presence, in the exudation in gonorrhœa, of peculiar micrococci, which occur as dumb-bells and as masses of dumb-bells either free in the serum, or frequently within the protoplasm of the pus cells, or adhering in smaller or larger numbers to the epithelial cells: these cocci he called gonococci (fig. 96). The length of a coccus is 1·25 μ, the transverse diameter 0·6–0·8 μ, and they occur, as just stated, in the form of diplococci and as groups of four; the cocci are crescentic, and in this respect do not differ from many other species of cocci (*see* Section A of this article). Besides these diplococci, cocci often occur in the pus of gonorrhœa which are spherical and probably belong to the staphylococcus species (liquescens albus and liquescens aureus).

The gonococcus does not grow on nutrient gelatine, on agar mixture, or potato, and herein differs materially from the ordinary cocci occurring in pus. Bumm has proved that the gonococcus grows only on blood serum, and Löffler and Krause have also succeeded in growing it on serum. In streak cultures on moderately solid blood serum and kept at 32° C., well moistened, the gonococcus, according to Bumm, grows in the form of a thin, narrow, greyish-yellow film, 1–2 mm. in breadth, with smooth and moist-looking surface. The growth does not proceed for more than a few days, and then dies. Animals are refractory against the gonococcus or the gonorrhœal secretion; dogs, rabbits, monkeys, horses show no reaction, either on the conjunctiva or on the urethra. Bumm has, however, succeeded in producing in the human subject real gonorrhœa by inoculating, from a culture of the gonococcus, the urethral mucous membrane.

There can be no doubt about the fact that the gonococcus which, as mentioned above, grows well on serum, is peculiar to gonorrhœa, and cannot, therefore, be confounded with other pus micrococci. Probably Neisser's gonococcus was only a pus coccus, since it grew also on other media.

Koch ('Cholerabericht,' 1883) has shown that what is spoken of as 'Egyptian ophthalmia' is really two kinds of infectious ophthalmias: one is an acute blennorrhœa or purulent ophthalmia, and does not differ from that known to occur in consequence of infection with gonorrhœal exudation.

Catarrhal Conjunctivitis (Koch).—A second, the true Egyptian ophthalmia, is, however, of an altogether different etiological character, though in its symptoms and pathology it is similar to, but not identical with, the blennorrhœa. This second one, the '*catarrhal conjunctivitis*,' is associated, not with the gonococcus, but with a minute fine bacillus, very similar in morphological respects to the bacillus of Koch's mouse septicæmia mentioned in a former chapter. In this ophthalmia the bacillus is present in the purulent exudation of the conjunctiva as isolated rods, but more commonly enclosed within the pus cells, whose protoplasm is sometimes found crowded with them (*see* fig. 97), in the same way as we saw the leucocytes in the mouse septicæmia crowded with the small bacilli. The cultivation of these bacilli carried out by Kartulis (*see* below) shows that there exist definite differences between this and the septicæmia bacillus of mice.

Kartulis, besides describing minutely the symptoms and course ('Centralbl. f. Bact. und Parasit.,' Band I., No. 10, pp. 289–293), and the differential characters existing between blennorrhœa of the conjunctiva and the catarrhal ophthalmia, succeeded in cultivating the bacilli of the catarrhal or true Egyptian conjunctivitis. He showed that they do not grow on nutrient gelatine; on blood serum or on agar they grow well between 28–36° C., forming in thirty to forty hours small white punctiform colonies, prominent over the surface of the medium; when closely sown (e.g. in streak culture) they soon coalesce into a whitish grey band of a fatty glistening appearance; the margin of the band is wavy or crenated. Animals inoculated on the conjunctiva with the conjunctival secretion or with the culture prove refractory; but Kartulis succeeded in producing with the culture the typical catarrhal conjunctivitis in one out of six cases in the human subject. The pus corpuscles resulting in this case were crowded with the characteristic bacilli. This one case was that of an individual twenty-five years old.

Xerosis Conjunctivæ.—Under this name is understood an inflammation of the conjunctiva associated with the secretion of whitish, fatty scales and clumps, consisting of fatty, degenerated epithelial cells with a few leucocytes. In these scales certain minute bacilli have been demonstrated by Kuhnbert and Neisser, Leber, Schatz, and others, in large numbers, almost in pure cultures; these were assumed to be the microbes of the xerosis. Schleich, Sattler, Fränkel, and Franke found them, however, in the secretion of the most varied inflammations of the conjunctiva and cornea, in trachoma, in corneal abscess, and in suppurations of the eyeballs; and Schreiber has definitely established that, not only do they occur in many diseased conditions of the eye, but also on the normal conjunctiva: this view is in harmony with that expressed by Weeks and also Fick, viz. that the xerosis bacillus is a common saprophyte, which owing to the pathological conditions in the eye finds an excellent medium and suitable conditions for its copious multiplication.

CHAPTER XVIII

ACUTE EXANTHEMATA

THE diseases belonging to this group are: (1) foot-and-mouth disease; (2) small-pox and vaccinia, and chicken-pox; (3) scarlet fever; (4) measles and rubeola; and (5) typhus fever. Strictly speaking, we ought to include here also erysipelas, but this has been treated already in a former chapter, together with the septicæmic diseases.

FOOT-AND-MOUTH DISEASE

This acute infectious disease affects cattle, sheep, pigs, and man. In cattle, after a sudden febrile rise of temperature and general constitutional disturbance (falling-in of the flanks and falling-off in feeding) there appears great salivation of a mucoid viscid saliva, at the same time on the mucous membrane, and about the lips, the mouth, the gums, and also the tongue, there are visible red papules of irregular shape, which in a day change into vesicles or blebs; these blebs have only a very short duration, since by the breaking of the superficial layer—the cover of the bleb—due sometimes to mechanical causes, they are changed into ulcers; the mucous membrane surrounding the ulcer is injected and the base of the ulcer is slightly depressed and often bleeding; in a few days the ulcer becomes covered with a thin cuticle, and then begins to heal; the whole is slightly depressed. While this eruption appears in the mouth a similar change occurs in the skin of the cleft between the hoofs and in the soft skin near the margin of the hoofs, the skin being at first swollen and injected, then a distinct vesiculation taking place, this by bursting becoming changed into a sore. These sores are very extensive, comprising in many instances the whole of the skin of the cleft between the hoof, and also extensive areas at the side and above the hoofs; the margin of the sore is tumid; the base of the sore dark red and bleeding. These sores produce, of course, lameness of the extremity; the animals move with difficulty and with pain; when both hind or both fore extremities are involved, movement is well-nigh impossible. These ulcerations last for several days, during which time the animals do not feed well, do not ruminate, and do not move; sometimes the extent of these ulcerations is very great, and the animals are then in a very helpless and pitiful condition.

In the sheep the eruption in the mouth is not so common as in cattle; in most cases it is limited to one extremity; here it is of the same nature as in cattle.

In pigs the eruption is most intense about the snout; sometimes sores of the size of a shilling and a florin being observed; the eruption is present on the feet at the same time.

In the human subject, foot-and-mouth disease shows itself as a febrile disorder associated with and followed by a red papular eruption of the skin on the hand and fingers, more rarely the toes and dorsum of the feet, and on the lips and the mucous membrane of the mouth, fauces, and pharynx. The papules are situated on an injected basis and become small blisters, then dry up into a thin crust, underneath which is a sore, which in a few days, as a rule, heals up; in rare cases the ulceration in the mouth is more of a diphtheritic character, and then runs a much longer course.

In respect of the intimate pathology of the eruption of the skin and mucous membrane, the following have been shown:[1]—

Sections made through the entire vesicle and the skin adjacent to it show the following (*see* fig. 31): In the central region of the vesicle, the superficial corium and the papillæ are densely and almost uniformly infiltrated with round cells, and similar cells surround all vessels throughout the entire thickness of the corium. In the peripheral portions of the vesicle the infiltration is less marked, and is not found at all in the skin bordering the vesicle. In some of the enlarged (thickened) papillæ, besides the round cells, isolated red blood-corpuscles are met with, and even ruptured blood-vessels with hæmorrhage. The vesicle is loculated and made up of a number of smaller and larger cavities, extending through the whole thickness of the rete Malpighii; in the centre the cavities are largest and longest, reaching in a vertical direction from the superficial corium to the stratum corneum of the epidermis. The septa between the cavities are strands of compressed epithelial cells of the rete Malpighii. As the disease progresses these septa are broken, and the cavities enlarging ultimately break through and open on the free surface; in consequence of this an ulcer is established. The contents of the vesicle are a fibrinous fluid: in it are numerous round cells, detached epithelial cells and their nuclei, many in a state of degeneration.

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[1] *Report of the Medical Officer of the Local Government Board*, 1885, p. 122 *et passim.*

The whole disease is then an acute inflammation of the corium and papillæ, leading to the exudation of round cells and fluid into the corium, the papillæ and the stratum Malpighii, in which latter cavities are established, gradually enlarging and becoming confluent.

In the mouth the eruption has the same character, except that the cavities formed within the epithelium are not so large and well marked; hence the vesicle is not so conspicuous; but there is here the same dense infiltration of the mucous membrane and of the epithelium, with lymph and leucocytes, and after the rupture of the superficial epithelium an ulcer of the mucous membrane is established.

That the disease is transmissible from the cow to human beings by the milk has been proved by various outbreaks, investigated and described by Dr. Thorne Thorne (Reports of Medical Officer, Local Government Board), and that it is also transmissible by direct contact is known to veterinary surgeons, who, by inspection of, and attendance upon diseased cattle, have been known to have contracted the disease on the skin and in the mouth. The way, however, in which the disease spreads from animal to animal is not well understood; that it does so spread easily and sometimes with great rapidity, of this there is unfortunately abundant evidence, and for this very reason it is so much dreaded by farmers. If in a herd of cattle an animal shows the disease, there is little chance that after a few days many will be found free of the disease; in a flock of sheep, one diseased animal means in many instances the majority of the flock. That the saliva of a diseased animal, that is, an animal affected with the eruption in the mouth, produces the disease by contact with the healthy mucous membrane of the mouth in another animal, for this there is but fragmentary experimental evidence. Mr. Duguid and Dr. Sanderson in 1874 made a number of direct experiments by rubbing hay, moistened with the saliva, taken from cattle affected with the eruption in the mouth, into the mucous membrane of the mouth of healthy cattle, but only in one single instance did they succeed in producing the disease. In this single instance the infection may have been produced, not by the direct contact at all, but by way of the stomach or intestine, or the respiratory tract. It is more feasible to assume that infection is carried out by animals while feeding on grass or hay, or licking articles which have been tainted with the diseased matter of the mouth or feet of affected animals and thereby introducing the virus into their system by the alimentary canal or the respiratory tract; this would be in harmony with what actually occurs in the human subject, e.g. by milk. The eruption being in the mouth and on the feet does not and cannot of course mean that the contagium has been introduced at those places, either in animals or in man; this is no more the case in foot-and-mouth disease than in small-pox, but like this latter is a result of the general infection of the system with the virus. In experiments which the writer has made with the microbe of the disease presently to be described, the typical disease on the feet of sheep was produced by feeding.

When fine sections through the vesicle (at its full development, and before it is broken) of the eruption in sheep are made and well stained, one finds in the contents of the vesicles amongst the leucocytes and the fibrinous and the albuminous material, cocci arranged as diplococci and as chains, streptococci: their diameter is about 0·2–0·4 μ; similar cocci can be demonstrated also amongst the epithelium cells below the vesicle, i.e. those in contact with the corium. From the contents of such vesicles, at their full development, and before they are broken, the writer has isolated by cultivation these streptococci. In the manner in which they form chains when growing in fluid medium (broth) they resemble other streptococci, e.g. streptococcus pyogenes, except that the cocci in the foot-and-mouth microbe are very much smaller and the chains are more wavy; also in the way in which they grow on the surface (streak and plate cultures) and in the depth (stab culture) of nutrient gelatine, on and in agar, and on solid blood serum, the streptococci of foot-and-mouth disease resemble other kinds of streptococci, e.g. the streptococcus pyogenes, the streptococcus of scarlet fever, &c.; but on nutrient gelatine the streptococcus of foot-and-mouth disease grows much more slowly than the others mentioned just now: the colonies are smaller, and are conspicuously more transparent than those of other streptococci. On making a streak cultivation on the surface of gelatine, the line of inoculation becomes noticeable after a few days, as consisting of very minute dots, not confluent; the whole growth is very transparent as compared with a similar growth of streptococcus pyogenes.

With broth cultures of the streptococcus of foot-and-mouth disease the writer has by feeding sheep been successful in producing the typical disease, viz. typical vesicles on the feet.

The same streptococci as were used for the feeding were again recovered by culture from the vesicle of the artificially infected sheep. So that it may be considered as established that the streptococcus present in the lymph is the actual microbe of the foot-and-mouth disease.

Schottelius quite recently (1892) observed in the lymph of the vesicles the presence of streptococci, which he, however, calls streptocytes, but from his description there is no necessity for considering them other than streptococci.

HUMAN VARIOLA

Pathology.—The eruption of the skin known as small-pox commences as a small localised swelling of the congested skin, in fact, as a minute firm papule, the swollen skin forming the papule, as well as the skin immediately surrounding it, being much congested and red. Next, the papules enlarge in thickness and breadth, and at the same time show in their marginal part clear evidence of vesiculation; the centre is less prominent than the marginal vesicular portion, hence a characteristic 'umbilication' is apparent. Next the vesiculation extends over the whole pock, which hereby loses its umbilicated aspect and becomes convex, the centre as convex as the marginal part, that is to say, the whole pock is converted into a flat or slightly acuminated vesicle. The vesicle at first contains clear lymph, which soon becomes turbid owing to the presence in it of numerous leucocytes or pus cells. Next, the vesicle dries up, the covering and contents becoming converted into a brownish crust; at this time the injection of the skin surrounding the pock becomes more marked, thus forming a more or less broad areola. In a few days the crust becomes loose, the parts underneath being slightly moist (purulent), and red; finally it contracts and heals, and the place of the former pock is indicated by a slightly tumid reddish mark. This course is, however, only noticeable in the milder cases; in severe cases the pocks are so closely placed—face, arms, and legs—that when they enlarge and become changed into vesicles these become in many places confluent, and such confluent patches sometimes measure an inch to two inches or more in breadth in one or the other diameter. Such confluent small-pox cases are always marked by a deeply congested skin surrounding the vesicles, and also by this, that when the vesicle dries up into a yellowish or brownish scab, and after this has become loosened and detached, an extensive ulcer is established, the surface of which is entirely denuded of the epithelium and the superficial or papillary layer of the cutis, and is covered with, and infiltrated by purulent matter; when this ulcer heals it always leaves behind a reddish cicatrix, at first raised beyond the surface of the surrounding skin, but by-and-by shrinking and becoming converted into a pale whitish pitted cicatrix. In malignant forms of small-pox the lymph of the vesicle at its first appearance is not a colourless, transparent fluid, but is more or less deeply stained by blood, the skin itself surrounding the vesicle containing blood effused in its tissue. This is the hæmorrhagic form, and is due to rupture of blood capillaries in the superficial parts of the corium both in the region of the pock as well as that surrounding it. Sections through the pock in its various stages show the following features: (*a*) in the stage of the papule: the blood-vessels of the corium and papillæ are distended and injected, more in the corium of the papule itself than in the corium immediately surrounding it; the papillæ themselves are enlarged, being both thicker and longer; in their tissue numerous lymph cells are already noticeable; the stratum Malpighii of the epidermis is thickened, owing to a rapid multiplication of its cells, and also to distinct swelling of the cells of the middle layers. In a vertical section the stratum Malpighii in the region of the papule is twice the thickness of that of the surrounding skin; the interstitial spaces, i.e. between the epithelial cells, particularly those in the upper layers of the stratum Malpighii, are very conspicuous by their breadth. (*b*) In the stage of the vesicle, the first indications of vesiculation are shown by the appearance of microscopic cavities, round, irregular, or elongated in the upper layers of the stratum Malpighii *in the marginal region* of the papule, hence the pock appears umbilicated; these spaces and cavities are entirely due to the enlargement of the interstitial spaces between the epithelial cells. Owing to the congestion of the vessels of the superficial corium and the papillæ we are justified in assuming that a considerable amount of lymph exudes, not only into the tissue of the corium—hence the swelling of the corium—but also into the epithelium, and for this reason the intercellular spaces become more apparent; and, further, as this exuded lymph passes outwards, it will accumulate between the cells of the more superficial layers of the stratum Malpighii of the marginal part of the pock, the dense horny layer above, i.e. the stratum lucidum and corneum, forming a barrier to the further passage. Owing to this accumulation of lymph, the intercellular interstices change into cavities of various sizes, and the epithelial cells themselves become involved, some being compressed, and others gradually swelling up and disintegrating. As the exudation of lymph proceeds, so the superficial layers of the stratum Malpighii of the marginal part contain more and more of those cavities, while the epithelial cells themselves become greatly disorganised; the cavities while enlarging become closer and longer, and ultimately become more or less confluent, separated only by streaks and septa which are the remnants of the former epithelial cells. The presence and increase in numbers and size of these marginal loculi, filled with lymph, produce the marginal vesiculation, the normal skin forming to a certain extent a barrier to the progrss of the vesicle; the further progress of the exudation will produce accumulation of lymph also toward the central part of the pock; hence cavities, filled with lymph, become established in the superficial parts of the thickened stratum Malpighii, and this causes the disappearance of the central umbilication of the pock. The exudation of the lymph proceeds from the engorged vessels of the corium and papillæ of the pock, and thereby the cavities in the stratum Malpighii become more and more enlarged, so that almost the whole of the middle and upper layers of the stratum Malpighii become converted into larger and smaller cavities, some confluent, others separated only by thin trabeculæ and septa: these latter are composed of the remnants of the former epithelial cells, some of them compressed into non-nucleated strands, others still showing a remnant of a nucleus, but their substance opaque or breaking down into granular *dêbris*. The cavities constituting 'the vesicle' contain 'lymph,' which in the hardened preparation is in a coagulated state: it contains numerous threads of fibrin, and in its first appearance, in the marginal part, a few lymph cells, and also more or less *dêbris* of broken-down epithelial cells are to be noticed. As the central part of the pock becomes also vesiculated, the number of lymph corpuscles present in the cavities is greatly increased, and this gives to the lymph the opaque or purulent character, and constitutes the stage of the pustule. (*c*) During the formation and progress of the cavities in the marginal, as also in the central part of the pock, there is great emigration of leucocytes from the blood-vessels, so that the deepest layer of the epithelium, the tissue of the papillæ and of the superficial corium all become infiltrated with crowds of leucocytes. Their passage from the papillary layer between the cells of the deepest layer of the epithelium, and further into the cavities in the middle and superficial layers of the stratum Malpighii, can be easily traced; at the same time they invade the epithelial cells themselves and help towards their destruction.

(*d*) The stage of the crust. When, as is the case in mild forms, the vesicle dries up as a whole and is converted into a crust, we find that beginning with the margin a new stratum lucidum is formed underneath the cavities of the vesicle; that is to say, the deeper layers of the stratum Malpighii in the region of the pock become gradually separated from the middle and upper layers, those containing the cavities, by a layer of horny epithelium, so that the vesicle in the narrower sense becomes enclosed within two horny layers, one on the surface, the former stratum lucidum and corneum, and one in the depth, the new stratum lucidum and corneum. This condition it is which has given rise to the statement that the vesicle is developed within the layers of the stratum lucidum, an incorrect interpretation, in which the new horny stratum separating the lower layers of the stratum Malpighii from the vesicle is mistaken for a portion of the original stratum lucidum. The vesicle is now separated by a horny layer from the deeper parts, and its contents, therefore, dry up and become converted into a crust, which ultimately loosens and falls off, leaving no scar behind, the deeper layers of the epithelium and the papillæ having been preserved underneath the new horny layer. At the same time the congestion abates, and the exudation of lymph and leucocytes gradually decreases, and finally disappears altogether from the epithelium and the papillary layer.

But when, owing to the severity of the process, the enlargement of the vesicle proceeds and extends beyond the middle layers of the epithelium, and the infiltration of the epithelium and papillæ with pus cells continues, then the whole thickness of the stratum Malpighii becomes involved in the vesicle and the crust, and the tissue of the superficial layers of the corium becomes destroyed; a typical ulceration is the result, of which the final result is seen in a pitted, well-marked scar.

VARIOLA OVINA

In sheep-pox the pathology is the same as in variola of man, both in cases caused by inoculation with lymph taken from a previous vesicle produced by inoculation—so-called vaccine vesicle of sheep—and in cases of a general eruption, natural as well as artificial, as after injection of lymph into the vein of a healthy sheep. In the papular stage, the vesicular stage, the pustular and ulcerative stages, the microscopic appearances are the same, the duration of the different stages being, of course, different from those of human small-pox. The local pock produced by inoculation of lymph is slower in its development, and is much larger than that of the general eruption, reaching a size of one-half to an inch in diameter. The vesicles of the general eruption run a much quicker course, and are much smaller; those on the lips containing purulent lymph as early as the second or third day, so that from the first appearance of the cavities in the stratum Malpighii, in the marginal part of the pock, to the formation of the cavities in the middle part of the pock, not more than some hours intervene.

VARIOLÆ VACCINÆ

The spontaneous eruption on the teats and udder in cows of papules, leading to vesicles, and these again to brown or black-brown thick crusts, known since the days of Jenner, Ceely, and others as cow-pox, shows a pathology identical with human variola. During the last two or three years the writer has had the opportunity of studying such spontaneous cow-pox in Gloucestershire and in Surrey. The first symptoms consist in the presence of red papules on a tumid injected skin; the size of the papules is in some places not more than that of a split pea, in others that of an ordinary pea; the skin is tumid and much injected. In a day or two after their appearance the marginal part of the papule begins to vesiculate, and is of light colour, while the centre is dark and umbilicated; the vesicle is distinctly surrounded by a sort of areola. In another day or two the whole papule is a vesicle, at first loculated, but soon continuous, the whole eruption having at the same time become much enlarged. The lymph which can now be squeezed out of the vesicle after breaking the superficial horny cover is clear, and under the microscope contains few lymph cells. But soon the lymph becomes purulent as the lymph cells increase in numbers; then the whole vesicle dries up into a brownish black crust which gradually thickens, the pock enlarging all the time, the corium itself being tumid and infiltrated; the scab remains firmly adhering, and continues to increase in thickness for about a week; the surrounding skin is at first much injected, but gradually becomes paler. Not till the beginning or middle of the third week does the scab show any signs of loosening; after this it begins to loosen, and finally becomes altogether detached, leaving a scar behind; the time of falling off differs in the same animal considerably, some extending over five to six weeks. Underneath the crust is a sore, covered with purulent matter; this ulcer only slowly and gradually contracts and dries up, becoming finally converted into a scar, at first reddish, but gradually becoming pale. If the crust is forcibly taken off while it thickens, a new crust is formed on the ulcer. As to the microscopic appearances, they are essentially the same as in human and sheep variola: the microscopic character of the papule, the first formation of the loculated vesicle, the extension of the vesicle over the whole pock, the purulent change of its contents due to the presence and increase of leucocytes, the condition of the epithelium, of the papillæ and corium in their different stages, the changes leading to the formation of the ulcer, and the character of the scab, all these are essentially the same in both processes.

By inoculation of lymph taken from the vesicle during the first week, or by using a young scab not later than the tenth day, and inoculating it into fresh cows or calves, typical vaccinia is produced, such as is well known since the days of Jenner, Ceely, Chauveau, and many others. For illustration of the appearances of the various stages in the calf, *see* the writer's paper in the Report of the Medical Officer of the Local Government Board, 1889.

Likewise inoculation of susceptible milkers into a cutaneous wound—generally the skin of the hand—produces at the place of inoculation an eruption known as human vaccinia, which in all essentials is identical with that of the cow or calf: the formation of the papule (third day); the gradual enlargement of this and the formation of an umbilicated loculated vesicle with dark centre (sixth to eighth day); the formation of the surrounding areola; the extension of the vesiculation over the whole of the enlarging pock (ninth or tenth day); the purulent change; the drying up of the vesicle into a dark brown gradually thickening crust, and the presence underneath it of a deep red sore; the loosening and ultimate falling off of the crust; the contraction and healing of the sore, and the leaving behind of a pitted mark, at first reddish, gradually becoming pale or white; all these are the same as in the calf.

Using lymph or crusts, after the purulent stage has set in, an eruption is produced both in the calf and in man, which runs a more rapid course, and is of a milder character than the above. Retrovaccination of the calf with lymph taken from a human vesicle not later than the eighth day produces typical results. The microscopic nature of the inoculated vaccinia is identical both in the calf and man: the nature of the papule, the formation of the vesicle, or rather loculi of the vesicle, the gradual enlargement of this and extension over the whole pock, the purulent change, the microscopic character of the changes in the epithelium, corium, and papillæ, are in all respects the same.

Various eruptive diseases on the teats and udder of the cow have been described by veterinary surgeons as true cow-pox, but on careful investigation, they do not bear this interpretation. Jenner and Ceely have already distinguished some such eruptions as 'false' cow-pox. In all of these eruptions it can be shown that they are contagious and spread from animal to animal, generally by the instrumentality of the milker's hands in the act of milking, being as it were transferred from the infected teat of one cow to the teat or udder of a healthy animal, a chap or any abrasion of the epidermis in the latter animal being the seat of the inoculation, which is generally followed by the appearance of a red pimple. In some instances this pimple, while enlarging, vesiculates more or less perfectly, and further changes into a brown crust, underneath which an ulcer of the corium is present. But the duration, general character, and course of the disease in the cow are not the same in all these eruptive diseases: in cow-pox it is of one kind, in the Hendon disease of another, and in the Edinburgh disease of a different kind.[1] The duration of the different stages, the nature and aspect of the ulcer underneath the crust, the period of healing, and the general condition of the cow, are different in these several diseases. Inoculations with matter taken from one kind of eruption or another produce different results both in man and in calves. The lymph or the crust of real cow-pox before the end of eight days, when accidentally inoculated into the hand of a susceptible milker, gives rise to typical vaccinia, i.e. a red papule on the third day, a well-marked umbilicated loculated vesicle with dark centre and surrounded by an areola on the sixth to eighth day, and a pitted white mark after the sore has contracted and healed. Lymph or crust taken from such a vesicle during the sixth to the eighth day, and inoculated into calves or susceptible human beings, always produces true and typical vaccinia. If lymph or crusts are used after the tenth day, an accelerated eruption is produced: the pocking and redness are marked as early as the second, vesiculation on the third day, purulent change very soon after; the crust is thin and becomes loose by the end of the week; the corium underneath is only slightly infiltrated, and soon heals: no distinct scar is noticed several weeks after.

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[1] A further eruptive contagious disease in the cow may be added, which was produced artificially by the writer with the bacillus diphtheriæ. *See* a later chapter.

If lymph or crust be used from the eruption on the milker's hand, which eruption had been contracted from natural cow-pox, and if such lymph be retrovaccinated on calves, the result is typical vaccinia (Jenner, Ceely). The illustrations given in the Report of the Medical Officer of the Local Government Board for 1889 show such a result. Calves vaccinated successfully, i.e. in which the process takes the typical course, are refractory to a second or revaccination.

Two other eruptive diseases on the udder and teats of the cow, which the writer had the opportunity of investigating, proved themselves to be different from cow-pox, though veterinary surgeons and others were and still are inclined to consider them all as 'cow-pox.' One of these was a contagious malady in cows at a Hendon farm. It was proved by Mr. Power and the late Dr. Cameron that the milk of certain cows of this farm had produced human scarlet fever in the north of London about the end of 1885 (*see* a further chapter). These cows were affected with an eruptive disease on the teats and udder, which though offering a certain resemblance to cow-pox was, nevertheless, distinctly different from it; the similarity consisted in the fact that the eruption appeared on the teats and udder, that it commenced as red papules, that it showed vesiculations, and that these dried up into brown-black crusts covering the sores; but here the resemblance terminated. The difference was manifested by the conspicuously more rapid course of the eruption than in cow-pox, by the greater infiltration of the corium at the eruption, by the fact that unlike cow-pox the eruption was not communicated to the milkers' hands, and by the important visceral lesions that the Hendon cows suffered from: these will be described in a further chapter. Inoculations with matter from the eruption into calves produced in them results which were also different from those produced in calves by vaccination.

A second eruptive disease in cows which was investigated was very similar to the one observed at the Hendon farm; this disease affected cows in Edinburgh, the milk of which had been proved to have produced febrile sore throat in the consumers. The eruption passed through a more rapid course than cow-pox, was not communicated to the hands of the milkers, produced on inoculation into calves a disease different from vaccinia, and was also associated with definite visceral disease in the cow. This will be more fully described in the chapter on SCARLET FEVER.

Towards the end of 1887 Dr. Crookshank described, before the Pathological Society, cases of eruptive disease on cows' udders and teats, occurring in Wiltshire, and which owing to the fact that the disease was communicable to the milkers' hands, on which it had produced vesicles resembling vaccinia, he felt convinced to be the 'true Jennerian cow-pox.' The proof which he then adduced as to the Wiltshire disease being true cow-pox rested on the facts (1) that the disease communicated to the milkers' hands resembled vaccinia; (2) that calves retrovaccinated from such a milker's vesicle developed at the insertion 'typical vaccinia;' (3) that these calves failed on revaccination with true vaccinia; and (4) that the milkers (at the Wiltshire farm) who had contracted the eruption from the cows failed afterwards to take 'vaccinia.' It is quite possible, or indeed probable, that the Wiltshire cow disease was true cow-pox; but neither at the time Dr. Crookshank first asserted it to be so, nor later on, did he furnish satisfactory or sufficient evidence for it. The assertion by Dr. Crookshank that the calves which were inoculated from a milker's vesicle did really develop 'typical vaccinia' turned out afterwards to be unreliable, since out of four of such calves three, on subsequent vaccination with real cow-pox a few weeks afterwards, at the Government Animal Vaccine Station, took typical vaccinia; a result which could not occur had these calves really had vaccinia previously. From the vesicles[1] produced at the animal vaccine establishment in one of these three animals children were vaccinated with typical results.[2] After the success of this second true vaccination of the calves had been made clear, they were declared by Dr. Crookshank not to have been sufficiently well vaccinated in the first instance, and therefore were not protected thereby against a second vaccination.

It must be obvious that evidence adduced by Dr. Crookshank in *subheads* 1, 2, 3 and 4 is not direct experimental evidence, and cannot therefore be considered as unassailable; that mentioned in *subhead* 3 was the only direct evidence that could be experimentally tested: this was done, and, as we have just seen, broke down completely.

The writer is inclined to think that the Wiltshire disease was probably true cow-pox; but that Dr. Crookshank in inoculating the calves from the milkers' hands failed to produce in them this disease.

Jenner from his own and previous observations has shown that natural cow-pox bears a definite relation to human variola: the first protects against the latter, in the same way as one mild attack of variola protects against a second virulent attack, or as in some other infectious diseases one mild attack protects against a second attack; all protective inoculations, such as in anthrax, charbon symptomatique, hydrophobia, fowl cholera, &c., are well founded on experiment, and often practised with great success. The facts observed by Jenner and Ceely, confirmed by a host of other observers, well qualified to judge from special knowledge and a life-long experience, viz. that natural cow-pox protects the cow from a second vaccination; that one successful vaccination protects the calf against a second inoculation; that persons (milkers) who have contracted the eruption on their hands or other parts from handling the teats of cows affected with the natural cow-pox become insusceptible to small-pox; and, above all, the fact that persons efficiently vaccinated and revaccinated from the calf or with humanised vaccinia are protected against small-pox, require little additional proof. The intimate relation that has thus been proved to exist between cow-pox and human small-pox suggests that the two eruptions are two forms of the same disease, the former in its natural occurrence as natural cow-pox being the small-pox of the cow and of a mild character as compared with the human form, which is more virulent, and in unprotected or in insufficiently protected persons generally assumes a grave character.

The great similarity in the pathology of the two eruptions also offers considerable support to this. Ceely has shown by direct experiment that cow-pox is really small-pox in the cow, and he and Badcock, as is well known, have in several instances—the latter in a large number of instances—succeeded in producing the eruption of vaccinia by direct inoculation of lymph or crusts taken from human variola into the skin of heifers. The lymph of the latter was then used for producing in the human subject typical vaccinia, which has been subsequently propagated as vaccinia for many generations of vaccinifers. Chauveau in his experiments, on the other hand, has failed; he maintains that he produced in the cow a papule, but the matter taken from such papule produced again in the cow only papules: in the human being, in some instances, it produced variola. But these negative experiments do not bring us nearer the decision of the question, any more than negative evidence ever does.

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[1] The companion calf was reinoculated with humanised vaccinia by Dr. Crookshank. Result doubtful. It failed on being inoculated afterwards with animal vaccine lymph.

[2] In a paper published by Dr. Crookshank in the *British Medical Journal*, July 1888, he states that this calf had practically failed on reinoculation at the Government Animal Vaccine Station. This statement is shown to be incorrect by the subsequent successful vaccination of children from this calf.

Voigt has also succeeded in producing vaccinia in the calf by inoculation with matter taken from human variola; and as was the case in Ceely's experiments, here also the positive result was achieved when, simultaneously, vaccinia was inoculated at a different part of the skin. True, the objection raised against these positive results as to an accidental introduction of vaccine matter, when only variolous matter was believed to have been used, is not an unfair one, and there can be, on scientific principles, no fault found with those who decline to accept it as conclusively proved, and free from any objection. But when some writers go so far as to say that because Chauveau and others (the writer amongst them) have failed to produce vaccinia in the cow by inoculating variolous matter, therefore it is proved that the two are essentially different eruptions, having nothing in common with each other; to these we are quite justified in saying, in opposition, that such a conclusion is not warranted, nor is it quite in harmony with the facts. Any number of failures incurred by one experimenter do not disprove the success of another, even if obtained in a single instance, any more than any number of negatives disprove one single positive; all that the failures prove is that the positive result is difficult of achievement and that the conditions under which it is or can be achieved are not known, but depend on chance. In the writer's report on inoculation of cows with variola (Medical Officer's Report to the Local Government Board, 1878) he has shown that by such inoculation of the cow some refractory condition against vaccinia is obtained, so that from this it must be concluded that a correlation between the two eruptions did exist.

Quite recently Fischer (' Münch. med. Woch.,' 1890, No. 43) has succeeded in producing in two calves an eruption by inoculation with human small-pox; the lymph of the eruption of these calves was transmitted through a series of other calves; from these lymph was obtained which, inoculated into infants, produced typical vaccinia. Two other experimenters (Dr. Simpson and Dr. King) have separately and independently, in India, produced vaccinia in the calf by inoculation with human variola.

Microbes.—Chauveau was the first to show by carefully arranged diffusion-experiments, that the active principle of sheep-pox and of vaccinia is particulate matter. Coze and Feltz, Hallier, Zürn, Cohn, Burdon Sanderson and others, have demonstrated in vaccine lymph the presence of bacteria, bacilli, and micrococci. The writer has shown the presence of micrococci in sheep-pock lymph, and in the lymphatics of the corium of sheep-pocks; F. Cohn, and then Weigert, showed the presence of micrococci in the lymph and lymphatics of human variola. Only comparatively recently, after the methods of cultivating micro-organisms had been perfected by Koch, has it been possible to isolate the different species of bacteria occasionally but not invariably present in variolous and vaccine lymph. Before giving the results of these cultivation experiments it is necessary to state that various observers have found torula-forms in the variolous lymph (Hallier), and in the vaccine (L. Pfeiffer). These torula-forms are, however, admittedly only accidental contaminations derived from the air.

Of the micrococcus forms—accidental and occasional inhabitants of lymph—that have been cultivated by L. Pfeiffer are various sarcinæ: sarcina lutea sarcina tetragonus, sarcina aurant. and muscopus. Of bacilli there have been occasionally found in calf lymph, seldom in lymph of children, short motile rods, liquefying gelatine, and most probably comparable to Hauser's proteus vulgaris—the common putrefactive bacillus. Of micrococci there are two species which, both in clear and in turbid preserved lymph of vaccine and variola, are occasionally met with; viz. the staphylococcus pyogenes aureus liquescens and the staphylococcus cereus albus (non-liquescens). P. Guttmann, L. Pfeiffer, and Garré have described these two species as often occurring in preserved lymph. The writer has devoted considerable attention to the culture from human vaccine lymph of micrococci, and he finds that the lymph of a considerable percentage of tubes examined by him, lymph which was and remained perfectly 'clear' when tested by cultivation on gelatine, agar, solid blood serum or broth, was found to be free from any of those microbes; no growth of any kind appearing in the tubes. There was also a percentage of tubes, the lymph of which was 'clear,' but on cultivation yielded a few colonies of staphylococcus cereus albus. In the case of lymph which was labelled 'clear lymph,' no staphylococcus aureus could be demonstrated by cultivation; but in a certain percentage of tubes discarded as 'opaque lymph' there was present, sometimes in large numbers, the staphylococcus aureus alone, or with staphylococcus cereus albus; in some cases gelatine tubes or agar tubes inoculated with a trace of the lymph yielded innumerable colonies of them, particularly of the staphylococcus aureus. Cover-glass specimens of some opaque lymph revealed large numbers of cocci, single, as dumb-bells, or in clumps. In a small percentage of tubes containing opaque lymph the number of micrococci present was small, and could not account for the opacity; in one case of opaque human lymph the writer cultivated a streptococcus in pure culture. Garré had already met with streptococcus pyogenes in the lymph of pemphigus complicating variola; the streptococcus which the writer has cultivated in the above case of opaque lymph was certainly not streptococcus pyogenes; it grew much more slowly, and its colonies in gelatine were conspicuously transparent when compared with those of streptococcus pyogenes.

The writer had the opportunity of examining the lymph of a child in which vaccinia was complicated by erysipelas, such lymph having produced erysipelas in two infants vaccinated with it. From this lymph the streptococcus of erysipelas was cultivated without difficulty. Gelatine-plate cultivations made with the lymph brought forth a pure culture of this streptococcus in innumerable colonies. So far as can be seen from the literature of the subject, this is the first time that the streptococcus of erysipelas has been actually demonstrated in lymph.

Though some experimenters assert that they have produced true vaccinia on inoculation of calves with cultures of one or the other of the microbes, it will on careful examination be agreed that these alleged positive results are not, and cannot be accepted. Competent investigators ('Berlin. Reichsgesundheitsamt,' 1881) have altogether failed to produce such results. The matter then stands thus: The microbes which have as yet been cultivated from lymph (variola or vaccinia) outside the animal body, freed of all accidentally adhering animal matter, have not the power to reproduce the disease on inoculation into a suitable animal. After the numerous failures to cultivate on the usual media—gelatine, agar, solid blood serum, broth—any of the above bacterial forms from samples of 'clear' and very good and active vaccine, the writer is in full agreement with those negative assertions, and is prepared to say that the microbes hitherto demonstrated as being present occasionally in clear and particularly in turbid vaccine lymph have nothing directly to do with the contagium of vaccinia or variola. Moreover, the presence of some of them, particularly the staphylococcus aureus when abundant, as in some cases of turbid lymph, or that of the streptococcus of erysipelas, in vaccino-erysipelas, forms a serious, preventable, and objectionable admixture.

L. Pfeiffer ('Correspondenzblatt d. allg. ärztl. Intell.,' 340; Thüringen, 1887) describes in the epithelium of the pock of man and animals, a parasite belonging to the coccidia (sporozoa, Leuckart). This parasite is said to live and grow in the epithelial cells, and ultimately to form spores, in size not larger than micrococci. But nothing definite is as yet known about these alleged sporozoa, called by Pfeiffer 'monocystis epithelialis;' moreover, it seems that these alleged coccidia of Pfeiffer are due to pathological (dropsical) changes of the nuclei or the substance of the epithelial cells of the pock, which changes appear traceable through all intermediate stages from normal nuclei and the normal protoplasm, and that therefore Pfeiffer's interpretation of these changes as coccidia is not justified.

SCARLET FEVER

In this acute infectious disease the skin, the organs of the throat, and the kidney are the chief tissues implicated. (*a*) The eruption of the skin shows the following characters: hyperæmia and inflammatory œdema of the superficial layers of the corium; the epidermis (rete Malpighii) is thickened, due to an active multiplication of its cells, and the same holds good also for the hair follicles. Owing to the continued multiplication of the cells of the rete Malpighii also the stratum lucidum increases in thickness, and the subsequent extensive desquamation of the stratum corneum and stratum lucidum are due to the continued reproduction of the cells of the rete Malpighii.

(*b*) The kidney. In the early stages of the disease there occurs fibrous and hyaline degeneration of minute arteries and Malpighian tufts of the cortex; the nuclei of the epithelium covering the tuft and lining the Malpighian capsules are increased (glomerulo-nephritis); the epithelial cells lining some of the convoluted uriniferous tubules are swollen, granular, and opaque—parenchymatous nephritis. In some cases after only two days, in most, however, at later stages, there occurs interstitial nephritis, consisting in the aggregation of round cells (leucocytes) in the connective tissue around the arterioles and Malpighian corpuscles of the cortex; numerous such microscopic round-cell aggregations are to be found in the cortex, in some severe cases even involving large portions of the cortex. In such cases one or the other arterial branch is found blocked, and around it the tissue of the kidney, like a wedge-shaped infarct, is densely infiltrated with round cells, the uriniferous tubules with their epithelium in such parts being in a state of granular degeneration. In the organs of the throat in the typical cases, where there is ulceration of the fauces, the mucous membrane is found intensely inflamed, and showing the usual anatomical characters of hyperæmia, exudation of lymph and round cells, and finally loss of the epithelium and the papillary layer of the mucosa, i.e. the formation of an ulcer.

But in all cases that are subjects of a *post-mortem* examination, the spleen, liver, intestines, salivary glands, and pancreas, show more or less pronounced inflammatory changes.

Scarlet fever, as is well known, is a highly contagious disease, the contagion occurring in all stages of the disease. There exists, however, a diversity of opinion amongst sanitarians as to which is the most infective stage; while some maintain that contagion occurs in the later stages—during desquamation—others consider the desquamative stage of less importance in this respect than the earlier phases, i.e. the acute throat illness. That infection does take place in some cases during the desquamative stage, is well ascertained by the experience of many who have studied the subject, but it has yet to be proved that the contagion is as frequent in the later as it is in the earlier or throat stages.

Numerous epidemic outbreaks of scarlet fever are now known in which milk was the vehicle of the contagium. Up to 1881, a number of such epidemics have been described by Ballard, Buchanan, Jacob, Robertson, Darbishire, and many others; they have been carefully tabulated by Mr. Ernest Hart in the 'Transactions of the International Medical Congress for 1881,' and we need not further enter into them.[1] These milk epidemics are nowadays so easily recognised since the classical investigations of Ballard and Buchanan, that there is hardly a health officer in this country who has not had the opportunity, even during comparatively few years of his activity, to himself investigate, or become acquainted with such an epidemic. Whenever and wherever in any given locality a number of cases of scarlet fever occur simultaneously in different and distant households, having no intercommunication with one another—school, church, visitors—the first means of the spread of the contagium thought of is milk, and in all such epidemics on further inquiry it is found that milk (or cream) was actually the vehicle of the contagium. Secondary infection, i.e. cases which occur later and are due to direct contagion, are of course excluded.

Now, until 1882 all such milk epidemics were assumed to be due to infection of a particular milk supply from human scarlatina; it was assumed that either in the house of the milkman or the milkdealer, or at one or the other stations of the milk on its passage to the consumer, the contagium, derived from a human case of scarlet fever, was added to it. As a matter of fact, in the above-named tabulated account of milk scarlatina ('Transactions of the International Medical Congress for 1881,' vol. iv.) several epidemics are mentioned in which this mode of milk infection from a human source was clearly demonstrated. As an illustration may be mentioned the outbreak investigated by Dr. Robertson, of Keswick, in which the contagium had found access to the milk of a dairy closely adjoining a house where scarlet fever had existed for several weeks. The cows were milked, every night and morning, into an open tin can, which was carried across an open yard, past the affected house. The children who first caught scarlet fever in the locality played about the yard while in a state of desquamation. Subsequently, on a particular day a general epidemic of scarlet fever broke out in the town, between thirty and forty families being invaded. All those suffering from the disease received their milk supply from this particular dairy. Some member of every family supplied had on this day either a scarlatinal sore throat or scarlet fever. Other families supplied from a different source escaped the disease. A lodger had the milk raw for supper and was attacked.

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[1] It is really curious to find how little such milk-scarlatina epidemics are known on the Continent and, as a matter of course, how sceptical Continental sanitarians are as to a question so well understood in this country.

His landlady boiled her milk the same night and escaped. We must here observe that a large number of cases of scarlatina occurring on the same day, the inference from this fact is that on a previous day, when the children who were peeling from recent scarlet fever were playing in the yard, they conveyed the infection to the milk which was in their neighbourhood.

But epidemics of milk scarlatina have become known in which such a mode of infection, viz. from a human source, can most probably be excluded. As an illustration of this category of milk scarlatina may be mentioned the outbreak of scarlet fever in Oxford in the spring of 1882, recorded by Dr. Darbishire, in the 'St. Bartholomew's Hospital Reports,' vol. xx. The substance of Dr. Darbishire's report is this:—Three cows were kept by those who sold the milk, and nine houses, containing eighty-five persons in all, were supplied morning and evening; the milk was never stored, as there was generally barely enough at each milking for all the customers. In the house to which the cows and paddock belonged there was a case of diphtheria in a young lady; she was removed to the infirmary on March 1. The cowman had a child ill with scarlet fever in his cottage from February 27 till March 3. On March 3 Dr. Darbishire had this child removed to the hospital and the cowman's cottage thoroughly disinfected; the cowman left his cottage to sleep in lodgings near, the care of the cows having been handed over to another man, engaged for that purpose. Now, if the milk had become infected from either of these two cases (one diphtheria and the other scarlet fever), this must have occurred for the first before March 1, for the other before March 3; and as the period of incubation of scarlet fever is known to be, as a rule, less than seven days, it follows that March 3 being the last day on which the milk could have received the contagium from a human being, March 10 would be the last day on which scarlet fever could have been produced by that milk, and the majority of cases of scarlet fever would have occurred before that day, as one cannot assume that in all these cases the period of incubation would be protracted to such length as seven days. But mark what really did happen. Dr. Darbishire states that no case occurred till March 10, on which day two cases of sore throat and one case of scarlet fever occurred; on March 11, one case of sore throat; on March 12, two cases of sore throat and one of scarlet fever; on March 13, four cases of sore throat and two of scarlet fever; on March 15, one case of sore throat and one of scarlet fever; on March 16, two cases of sore throat and one of diphtheria; on March 17, one case of sore throat; on March 18, one case of sore throat. Now, all these cases were proved by Dr. Darbishire to have been caused by that milk. There occurred subsequently other cases, but these were shown to have been due to secondary infection from person to person. This is a good illustration of a milk epidemic in which the milk most probably was not fouled by human agency; and there are other milk epidemics which on analysis of dates lead to the same conclusion.

Then a third group of milk scarlatinas is known, in which infection from a human source could be definitely excluded; as an illustration of this Mr. Power's report in 1882 on an epidemic outbreak of scarlet fever in St. Giles and St. Pancras may serve. 'The disease was distributed with a milk service derived from a Surrey farm. In this case two facts could be affirmed: the one that a cow recently come into milk at this farm had been suffering from some ailment, seemingly from the time of her calving, of which loss of hair in patches was the most conspicuous manifestation; the other that there existed no discoverable means by which the milk which had coincided with scarlatina in its distribution could have received infective quality from the human subject.'

The Medical Department of the Local Government Board has from these facts drawn the conclusion that distrust must be placed on the universally accepted explanation that milk receives infective properties directly by human agencies,' and further that 'the question of risk from specific fouling of milk by particular cows suffering, whether recognised or not, from specific disease was seen to be arising.' This view received striking confirmation and proof by a report of an outbreak of scarlet fever that occurred at the end of 1885 and the beginning of 1886 in the north of London, and was investigated by Mr. Power. His report is published *in extenso* in the Report of the Medical Officer of the Local Government Board for 1886; and we will here give the substance of it. Mr. Wynter Blyth, Medical Officer of Health for Marylebone, had in December 1885 observed a sudden outbreak of scarlatina in his district to be associated with the distribution of milk coming from a farm at Hendon, and had found reason for believing that the disease had prevailed exclusively among customers furnished with milk from that source. Mr. Power, on a more extended inquiry, found that a similar prevalence of scarlatina had occurred about the same time in other parishes in and near the metropolis which were furnished with milk from the same farm. After careful inquiry Mr. Power could with certainty exclude any contamination of the milk from a human source, and say that nothing of the kind known as 'sanitary' conditions could have had any concern with the infectivity of the milk. Mr. Power showed conclusively that only certain sections of the milk supplies of this farm, and finally only certain cows from which these sections of milk were derived, had any relation to the observed results. 'In the end,' says the Medical Officer, 'he has demonstrated, beyond reasonable doubt, the dependence of the milk scarlatina, occurring from day to day during December, on a diseased condition of certain milch cows at the farm, a condition first introduced there in the previous month by some animals newly arrived from Derbyshire; and he finds strong circumstantial evidence for believing that the latter phenomena of this dependence were brought about through the extension of the diseased condition of one set of animals to another set, after the fashion of an infection.' Now, this disease as it presented itself in some of these Hendon cows consisted in the presence of sores and scurfiness in different parts of the skin, with loss of hair in patches, an eruption leading to the formation of a sore covered with dark brown scab or crust on the udder and teats, and a visceral disease, notably of the lungs, liver, kidney, and spleen, which, although milder in character. very much resembled the visceral lesions occurring in cases of human scarlet fever. By experiment it was shown that the matter of the eruption of the udder is possessed of infective power, inasmuch as on inoculation into the skin of calves the same eruption is reproduced.

The microscopic examination of fine sections through the eruption of the cow shows the following conditions:—

The corium throughout the whole extent of the eruption is infiltrated with round cells. This infiltration, though densest in the central portions of the ulcer, is sufficiently pronounced even in the peripheral parts, but it gradually fades away on passing from the ulcer to the normal skin. The infiltration in the deeper parts of the corium is limited to the vascular branches, but in the superficial parts is more diffuse, the papillæ becoming at the same time thicker. This thickening of the papillæ fades off towards the periphery of the ulcer. The most noteworthy changes are, however, present in the epithelium. In the peripheral portions of the diseased part there are present in the superficial layers of the stratum Malpighii close to the stratum lucidum, as also in the stratum lucidum itself, numerous cavities of different sizes.

These cavities lie closely side by side; the most superficial ones are either covered by the stratum lucidum, or extend between the layers of this stratum. The former cavities descend into the depth of the epithelium; at the very margin of the diseased part they are smallest, and they do not in depth comprise more than the superficial third of the stratum Malpighii. They gradually enlarge in depth as we pass from the periphery of the ulcer towards its centre; at its very centre they involve the whole thickness of the stratum Malpighii. At the same time it is to be noticed that, at the marginal parts, the cavities, although closely placed side by side, are well separated from one another by thicker or thinner trabeculæ composed of epithelium; while at or near the centre of the ulcer these trabeculæ get destroyed, and the cavities become confluent, and the covering layers of the cuticle having here also given way, their contents extend on to the free surface of the ulcer. These contents, which go to form what has been above mentioned as the crust, thus gradually spread over the surface, not only of the centre, where the stratum lucidum has become lost, but also over the rest of the ulcer. In the marginal portions, i.e. where the superficial layers of the cuticle are still present as cover of the above cavities, this layer (i.e. the stratum lucidum) separates the contents of the cavities from the crust. The contents of these cavities consist (*a*) of an albuminous fluid, looking, in hardened sections, uniformly granular, or containing also fibrinous threads; (*b*) of a few red blood-corpuscles; and (*c*) chiefly of round cells or pus cells, the nuclei of which, near to, and on the surface, gradually break up into amorphous granular matter.

In the central parts of the ulcer the whole exudation undergoes degeneration into *débris*, not only in its superficial, but also in its deeper portions. While some cavities contain very few cells, and are filled chiefly with albuminous fluid (granular or fibrinous), others are almost entirely filled with pus cells closely packed together. In the papillæ near the cavities the blood-vessels are engorged and there is also escape of red blood discs.

On a careful examination it is evident that the origin of these cavities is in enlargement of and exudation into the tissue of the papillæ, but only of those portions nearest to the stratum lucidum, and hence arises the formation of cavities in the cuticle. The whole anatomical details of the distribution and arrangement of these cavities vividly recall the conditions observed in the vesicles of cow-pock and of sheep-pock, and on comparing under a low power of the microscope a section through a sheep-pock with a section through the eruption of the cow now under consideration, the similarity is very striking indeed.

There are, however, anatomical differences between the two diseases. The infiltration of the corium is slighter in the cow eruption than in the sheep-pock, and in the cow-ulcer the cavities are situated in a more superficial stratum of the epidermis.

There is in the disease we are now considering a good deal of infiltration of the epithelium by round cells derived from the cavities, not only into the stratum Malpighii, but also, and particularly in the marginal parts, into the cuticle; the round cells burrowing in great numbers between the scales of this stratum, and ultimately reaching the free surface to join those of the crust.

Fine sections made through the ulcer artificially induced by inoculation in the ear of a calf proved its complete identity in anatomical respects with the ulcer in the cow. The infiltration of the superficial corium; the formation of cavities, filled with exudation cells and fluid, in the superficial layers of the epithelium, and particularly between the layers of the cuticle; the final destruction, in the centre of the eruption, of the covering cuticle; and the extension of the exudation over the free surface to form the crust, are the same in both instances.

The microscopic examination of the internal organs reveals facts as follows:—

In the Lung.—Sections made through portions containing much congested lobules show not only great congestion of the blood-vessels, large and small, but a large amount of hæmorrhage, blood in substance being present in the air vesicles and infundibula, in the lymph spaces of the interlobular septa, and in the tissue and lymphatics of the pleura. In the latter membrane numerous diplococci are to be met with. Here and there the same diplococci occur in the alveolar wall and in the tissue of the interlobular septa.

Sections through the *liver* show a great deal of change. Under the capsule, as well as in the substance of the liver, there occur, in connection with the interlobular branches of the portal vein, larger and smaller foci of inflammation, consisting in the presence of numerous round cells. Some of these foci are several millimetres in diameter, others are much smaller. From the interlobular tissue the inflammation extends into the lobules between the liver cells. The liver cells of these lobules involved in the inflammatory process are swollen up, and many of them are undergoing disintegration. In some of these foci, particularly those situated in the vicinity of the capsule, the round cells are so much crowded that given foci look almost like miliary abcesses. The blood-vessels are much distended and filled with blood.

Numerous diplococci and short coccus-chains occur in the parts surrounding the inflammatory foci. These are particularly numerous near the capsule in the vicinity of inflamed parts.

Sections through the *kidney* show well-marked glomerulo-nephritis; infiltration of the sheath of the cortical arterioles with numerous round cells; the epithelium of the convoluted tubules swollen, opaque, and in many places disintegrating.

Since this Hendon outbreak of ulcerative disease on the teats and udder of milch cows, connecting the milk with the outbreak of human scarlatina, several such outbreaks have become known and investigated: one was described by Dr. Russell, Health Officer in Glasgow, who traced the infected milk to cows which were affected with an ulcerative disease of the skin of the teats and udder; and the writer has become acquainted with one in the Camberwell district, London, where the scarlet fever was traced to milk coming from a particular dairy, in which at least one cow, at the time of the investigation (May 1888), was affected with sores on the teats. Calves were inoculated with matter (scrapings and scab) of such a sore, and it was conclusively proved that we had to deal with a contagious disease communicable to the skin of the calves, and leading on inoculation to the formation of ulcers of exactly the same kind as were produced in calves (in 1886) inoculated with matter from the sores of the Hendon cows.[1]

Now, the Agricultural Department of the Privy Council had in 1887 and 1888 taken an immense amount of trouble in the matter and came to the conclusion that the contention of the Medical Department of the Local Government Board, as to a direct connection existing between eruptive disease of the cow and human scarlatina, was not correct; that there exist contagious eruptive diseases of the cow which are not connected with scarlet fever in man; and on these grounds they formulated a direct negative to the contention of the Medical Department of the Local Government Board. Various deputies of the Agricultural Department found outbreaks of eruptive disease of the teats and udders of cows in various parts of the country, which disease, through the milk of those cows, had not given rise to scarlet fever; this disease was maintained by them to be identical with the Hendon disease, which had been connected with human scarlatina, although they had no direct knowledge of the Hendon disease, and judged merely by the fact that in the Hendon disease there was ulceration on the teats and udder. Dr. Crookshank made very definite assertions in this matter. The Wiltshire disease, which Crookshank maintained to be the true Jennerian cow-pox, was an eruptive disease that served the Agricultural Department as model for almost every eruptive disease of the cow, but forgetting at the same time that, though all eruptive diseases on the teats and udder of the cow may be similar in some, they are nevertheless dissimilar in other respects, and forgetting that it is not in the points in which they are similar, but in those in which they are dissimilar, that a differentiation amongst them is possible.

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[1] An extensive outbreak of scarlatina occurred simultaneously in several districts of the south of London between March 28 and the first week of April, 1892; all the cases of this outbreak were conclusively traced to milk coming from one particular dairy farm, A, at New Cross. As a most instructive natural experiment performed during this outbreak the following may be mentioned:—A milkman about Chislehurst, in whose district no cases of scarlet fever had occurred previous to March 28, had on that day

All the eruptive diseases on the cow's udder have this in common amongst themselves, that the eruption commences as a papule on an injected skin; that this papule while enlarging changes into, now a distinct, now a less distinct vesicle; that this vesicle, when formed, contains lymph which is at first clear and then becomes purulent; further, that the eruption becomes covered with a dark crust underneath which is a sore of the cutis; the crust thickens and ultimately becomes loose and falls off, the sore becoming dry, contracting, and healing. As said just now, all eruptive diseases in the cow have, speaking roughly, those points in common, and in Jenner's time and afterwards were all grouped into two great classes, viz. true and false cow-pox; and even to the present time dairymen, farmers, and veterinary surgeons in this country know only of true and false cow-pox.

The Agricultural Department declared that all contagious eruptions of the teats and udder in recent years were cow-pox, pure and simple, and therefore that the Hendon disease described by us was cow-pox, the same as the Wiltshire disease. When, however, the different eruptions are more carefully studied, it is found that they differ: (*a*) in the progress and duration of the eruption; (*b*) in the nature of the infiltration of the corium; (*c*) in the rapidity with which they heal; (*d*) in the results of inoculation into calves; (*e*) in the question whether transferable to the hand of the milker or not; and (*f*) lastly, but not least, as to whether the disease is simply a local disease, or whether it is associated with constitutional and visceral malady. Now, the Wiltshire cow eruption was possibly, one might even say probably, cow-pox, but the Hendon disease was certainly not; here the eruption ran a much shorter course, the infiltration of the corium was more pro-

added to his usual milk supply, owing to this being shorter than usual, a certain amount of milk from the dairy A of New Cross. A few days after (evenings of March 29 and 30) numerous cases of scarlet fever occurred almost simultaneously amongst the families in Chislehurst and Bexley supplied with this mixed milk. Now, in this dairy farm A at New Cross, fouling of the milk from a human source could with certainty be excluded; but a few days previous to the outbreak of scarlatina one cow had been ill: it was quiet, off food, coughed, its milk was ropy, and when seen about April 6 had two sores on the udder, covered with brown crusts; the sores were contracting and in a state of healing. Four other cows milked by the same hand had also sores covered with scabs on their udders.

nounced, the duration of the crust stage was considerably shorter, and the healing proceeded much more rapidly. The result of inoculation of calves was also different: the disease was not communicated to the milker's hands, and, as was shown above, there was distinct disease of the viscera.

The writer has shown that in the ulcers of the Hendon cows, and in the diseased portion of the viscera of these cows, there occurs a streptococcus that occurs also in human scarlatina (in the skin, in the blood), and which was called the streptococcus scarlatinæ. This streptococcus in culture and in morphological respects resembles other streptococci, amongst them the streptococcus pyogenes; but notwithstanding the numerous assertions to the contrary—that all or most streptococci are streptococcus pyogenes—our streptococcus scarlatinæ is by careful study capable of being distinguished from the streptococcus pyogenes. Experiments by feeding or inoculation made on calves and mice, made with the streptococcus scarlatinæ derived from the sores of the Hendon cows or of human scarlatina, produced definite general infection, and from such animals the microbe was recovered by cultivation: results which cannot be obtained with the streptococcus pyogenes.

hum

More than that, by inoculation of six milch cows with the human streptococcus scarlatinæ, a definite eruptive disease was produced on the skin generally, and on the teats and udder particularly, associated with visceral disease identical in every respect with the cutaneous and visceral disease observed in the Hendon cows. It is, we consider, proved hereby that the streptococcus derived from human scarlet-fever cases, producing as it did the Hendon disease in the cow, i.e. the same disease which was the source of infection in the human subjects in the Marylebone epidemic, must be considered as the microbe of scarlet fever.

Professor Axe, Dr. Thin, and also Dr. Crookshank, have made certain assertions—accepted by the head of the Agricultural Department—as to the milk at the Hendon farm having been really infected not by the cows but by a boy who carried the contagium from a human case of scarlatina to the farm, the boy himself supposed to be free of the disease. But no such boy could have infected the Hendon milk; besides, the milk of that Hendon farm, as in most instances in which the cow disease is the cause of the infectivity of the milk, had infective power from day to day for weeks (compare an article in the 'Practitioner,' March 1889).

It was asserted by Professor Axe and Dr. Crookshank that the Hendon disease could not have been other than the Wiltshire disease, i.e. cow-pox, because at the time of the Hendon disease, and afterwards, there existed in different parts of the country an ulcerative eruptive disease of cows which was communicable to the milker's hands as vaccinia, and of course was not connected with scarlet fever; indeed, the head of the Agricultural Department classed all the eruptive diseases together as the same, being probably cow-pox. This was strikingly illustrated in Dr. Russell's case in Glasgow; here the scarlet fever epidemic was traced to milk coming from a dairy farm where cows were affected with an eruptive ulcerative disease on the teats and udder. Professor Brown submitted to Dr. Russell drawings of ulcers on the udder and teats of cows as the Hendon disease, which were not drawings of what was understood as the Hendon disease, but of the Wiltshire disease. It need hardly be said that drawings of ulcers on the teats and udder of cows all look very much alike.

But though perfectly familiar as the Agricultural Department and the veterinary profession in general seemed to have proved themselves to be with the fact that all eruptive diseases of the teats and udder of the cow then prevailing in England (1885–1888) are one and the same, there occurred an outbreak of an eruptive disease amongst cows in Edinburgh (in 1887), which seemed to offer some differences and to make some rupture in that accepted uniformity of eruptive diseases.

During 1887 an eruptive disease appeared amongst certain cows in a dairy farm in Edinburgh, the milk of which had distributed amongst the consumers (in an educational establishment in that city) a form of febrile sore throat, which could not be recognised as either scarlatinal or diphtheritic. Dr. Sims Woodhead and Mr. T. M. Cotterill clearly proved the connection of this malady with the milk of that dairy farm; more than that, on the suspension of the consumption of the milk the epidemic quickly disappeared. When the use of the milk was recommenced sore throats of a similar character appeared again. Then all the milk was boiled before use, when the epidemic similarly yielded ('British Medical Journal,' June 9, 1888). Now the writer had the opportunity of receiving one of those cows, and he ascertained that the nature, progress, and duration of the ulceration on the teats and udder were quite unlike those of the Wiltshire malady, but similar to, though slightly different from, those observed in the Hendon disease. Inoculations of calves with the matter from the cow's sores yielded positive results. There was present in that cow a definite visceral disease (lung and liver). (Report of the Medical Officer of the Local Government Board for 1888.) From the ulcers of this cow a streptococcus was cultivated which also proved different from the streptococcus scarlatinæ; it was in culture very similar to the streptococcus pyogenes; it did not produce any specific result on inoculation into rodents, but on cutaneous inoculation into calves it produced strikingly positive results—ulceration and crusts of the same character as those produced directly by cutaneous inoculation of the ulcer material of the cow. Here, then, we had a further eruptive disease in the cow, differing from the Wiltshire disease and also from the Hendon disease, and connected by means of the milk of the cow with febrile sore throat in the human subject; there occurred no direct infection of the hands of the milkers, as in the Wiltshire disease. The above positive experiments on calves prove, we think, that this streptococcus was the microbe of the Edinburgh disease, and was different from the streptococcus pyogenes on the one hand, and from the streptococcus scarlatinæ on the other.

It was instructive to learn from a report by Professor Macfadyean, of Edinburgh, to the head of the Agricultural Department of the Privy Council that the Edinburgh cow disease was a different disease from the Wiltshire disease. But though the disease went on spreading amongst the cows, the milk of such cows was not consumed, or when consumed was first boiled and the throat epidemic ceased (*see* 'Practitioner,' March 1889).

In the next chapter a further eruptive contagious disease on the udder of cows will be described, but which in its progress and duration was no more, certainly much less, cow-pox than the Hendon disease, and which in its causation was no other than diphtheria, since it was artificially produced by subcutaneous injection of culture of the bacillus diphtheriæ.

In typhus fever, whooping cough, measles, rubeola, varicella, and Oriental plague, no definite microbes have as yet been demonstrated; in whooping cough, micrococci, moulds, and bacilli have been asserted to be associated with the disease, but no real satisfactory evidence is forthcoming; in measles, in Oriental plague, in yellow fever, and other specific diseases, micrococci are often met with and have been mentioned by many observers.

So also in the case of Beriberi; while some observers (Lander, Ogston) maintain that bacilli occur in the blood, and regard them as the microbe of the disease, others (Pekelharing and Winkler) claim micrococci in the blood as the real cause. Rinderpest is maintained by Metschnikoff and Gamaleia to be caused by a bacillus in some morphological respects similar to anthrax bacillus; these observers maintain that they have found

Plague B. discovered by Kitasato since -

the bacilli in the ulcers of the stomach and also in the blood of the affected animals. Further, they have cultivated the microbe and found it to grow on gelatine in a manner similar to the typhoid bacillus. Lastly, they assert that they have reproduced the disease in calves and guineapigs by inoculation of such cultures.

CHAPTER XIX

DIPHTHERIA

This acute infectious disease, to which children and young individuals are particularly prone, shows itself in most instances as a severe inflammation and fibrinous infiltration of the mucous membrane of the fauces and pharynx, or also the larynx and trachea, leading to, and early in the disease consisting in, a necrosis of the superficial part of the mucous membrane, and thereby changing this into a tenacious, whitish pseudo-membrane, the 'diphtheritic membrane.' In most cases only the mucosa of the fauces (tonsils, palatine arches, velum palati and uvula, upper part of pharynx) shows this change, i.e. into whitish grey 'diphtheritic membranes;' in other cases this necrotic change extends over the whole of the pharynx into the larynx, and even the trachea; in still other cases it starts in the larynx and invades this and the trachea—croup. In some cases a similar inflammation and the formation of diphtheritic membranes are observed in the stomach, in the intestine, in the urinary organs, and independently and primarily on wounds. In addition are to be mentioned myocarditis diphtheritica. The microscopic character of diphtheritic inflammation is generally this, that the mucous membrane is the seat of a severe inflammation and necrosis: engorgement of, and extravasation from, the superficial capillaries and veins, with stasis of blood in them, and swelling due to infiltration of the mucosa with fibrine and round cells; the epithelium as a whole is lost, the affected mucosa itself becomes necrosed and changed into a whitish-grey coagulated mass, in which fibrin, a close network of threads and septa, and in the superficial parts, lymph cells, may be recognised, this necrosed or coagulated portion forming the diphtheritic membrane; close to that part which comprises the necrosed mucosa, the outlines of blood-vessels filled with stagnated and coagulated blood, and extravasated blood, as also dense infiltration with lymph cells, may be recognised. When the process continues into the depth and breadth, this inflamed portion also becomes necrosed, and a part of the diphtheritic membrane. After the process passes the acme, the inflamed tissue, not necrosed by the exudation, gradually detaches the diphtheritic membrane above it, and an ulcer is left behind, which, like other healing ulcers, gradually contracts and becomes covered with healthy membrane and epithelium.

A section through a diphtheritic membrane shows a few nuclei in a dense, more or less fibrinous reticulated or hyaline matrix, more or less ill preserved; some of these take the staining, i.e. are not dead; in others already dead, the outlines can barely be recognised. In the superficial parts of the diphtheritic membranes a number of larger or smaller loculi are always seen, which are filled with clumps of bacteria (*see* illustration). These clumps of bacteria are of various kinds: staphylococci; streptococci, but not so common; thick and long septic bacilli, and groups of minute bacilli which we will call the diphtheria bacilli. These latter are found in larger and smaller masses on the surface, forming sometimes a continuous layer; in some cases sections show that in the middle, and occasionally, but rarely, even in the deep parts, they are the only bacteria present; here they are in small clusters, or they form large masses (*see* fig. 73). In the mucous membrane next to, but not part of, the diphtheritic membrane, the writer has found them occasionally in small numbers; in the inflamed mucous membrane of the depth these diphtheria bacilli are, as a rule, rarely to be found. In the blood and in the viscera the bacilli are absent; nor are other micro-organisms to be found as constant inhabitants. In cases of diphtheria ending fatally, even if the disease only lasted a few days, the lungs are the seat of severe bronchial catarrh, lobular or broncho-pneumonia; the kidney is congested and shows distinct parenchymatous nephritis, the epithelium of many convoluted tubes of the cortex is granular, disintegrating and fatty; in the liver, fatty degeneration of the liver cells is generally present. As to bacteria of diphtheria there are many assertions.[1] The one species that is constant and can be easily isolated in many cases in almost pure cultivation from the superficial and even middle layers of the fresh diphtheritic membrane are minute bacilli (see figs. 74, 75): some are curved, most are straight, some slightly swollen at each end, or knob-shaped at one end, many of them pointed at one end; in fact, this may be regarded as the typical bacillus. These bacilli occur either singly or in dumb-bells; many show a segregation of their protoplasm into granules or rods of unequal size; amongst these 'granular' forms, one or both terminal granules are occasionally club-shaped. Some of the single bacilli in well-stained specimens show a deeply stained granule at each end. The bacilli of agar cultures show the same appearances as those in the diphtheritic membrane; in gelatine culture the bacilli are shorter, thicker, and many are conical (*see* fig. 76). These bacilli were first seen by Klebs, and by Löffler were regarded, owing to their constancy, as pathognomonic and pathogenic for diphtheria; Löffler had first isolated them by culture on blood serum, but he, and then Hoffmann, found a morphologically similar bacillus in the normal discharges of the fauces. Now, Löffler maintained that, while the former or the 'diphtheria bacillus' is pathogenic for animals, the latter or pseudo-diphtheria bacillus is not so; but this has not been accepted by all, though, as we shall see, it nevertheless corresponds to the facts.

Besides, in true diphtheria of the fauces, the diphtheria bacilli can be demonstrated in many cases of croup, and in diphtheria *following* scarlatina, but not in so-called scarlatinal diphtheria, that is, in necrotic change in the fauces occurring simultaneously with scarlatina. (Löffler, Kolisko and Paltauf, Tangl, Klein.)

The bacillus of diphtheria isolated by Löffler forms colonies of definite characters on serum and agar plates kept at 35–37° C.: round white colonies, thickest in the middle and gradually assuming here a yellowish-brown tint. According to Löffler it does not grow on gelatine at temperatures below 20° C., but the writer has obtained cultures even at 19° C. on gelatine; on potato it shows no visible growth. Löffler found this particular bacillus in a large percentage, but not in all of the diphtheritic membranes; Kolisko and Paltauf, Roux and Yersin, Zarniko and Escherich, found this microbe in all cases of diphtheria, and owing to its peculiar pathogenic action (*see* later) they definitely regarded it as the microbe of diphtheria. The writer has shown that there occur in diphtheritic membranes two species of bacilli, identical in morphological respects and in the mode of growth on and in agar plates, on serum, and on potato; but one species is not constant, and is probably the pseudo-diphtheria bacillus of Löffler, while the other is constant in large numbers in all diphtheritic membranes; this second species is the one which is pathogenic, and is the diphtheria bacillus of Löffler, while the first one is not pathogenic. There is an important cultural difference between the two species; it is this: the true diphtheria bacillus grows well in and on gelatine at 19–21° C., the other does not grow on this medium below 22° C. Besides, the true diphtheria bacillus grows very rapidly in broth, making the broth (at 37° C.) uniformly and distinctly turbid in twenty-four hours. We shall therefore consider this as the Klebs-Löffler or true diphtheria bacillus, and it only remains to be added that on gelatine the bacillus can be easily isolated from the fresh diphtheritic membrane in numerous colonies; a particle of the membrane is first well washed and shaken successively with two or three successive quantities of sterile salt solution; from the last plate cultivations are then established (*see* illustrations).

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[1] Oertel, Nassiloff, Wood and Formad, and others as to micrococci; Von Emmerich as to short bacilli; Prudden as to streptococci.

On gelatine the colonies are at first rounded, white, prominent dots, which broadening, thicken in the middle and here become slightly yellowish in reflected, dark brown in transmitted light, the peripheral part being thin, plate-like, and angular; in streak cultivation on gelatine the streak becomes marked as a white band, at first made up of droplets, but soon becoming confluent into a uniform band; at the margin the droplets and knob-like expansions can still be recognised; the middle is thick and prominent; in stab culture in gelatine the stab becomes indicated by a line of droplets, white in reflected, brownish in transmitted light; the upper point of the stab is occupied by a crenate convex white plate. Of course on gelatine, at 19–21° C., the growth is much slower than on agar at 35–37° C. In milk kept at 20° C. our bacillus grows luxuriantly and produces after three days, or even less, slight curdling of the milk, and minute flakes of coagulated casein; at 37° C. the growth is curiously less abundant in the same space of time, and the curdling far less. The diphtheria bacilli are killed by heating to 60° C. for five minutes.

Löffler maintains that with cultures of the diphtheria bacillus, definite pathological results—inflammation with something like diphtheritic necrotic membrane—can be obtained by rubbing them into an abraded surface of the mucous membrane (mouth, trachea) of rabbits, fowls, pigeons, and Roux and Yersin make the same assertion; but such results are not obtainable either with human diphtheritic membranes, or with the cultures of the diphtheria bacillus; neither in the rabbit nor fowl, pigeon nor guineapig, in the mucous membrane or the skin has the writer been able to produce any result that at all resembles diphtheria. If occasionally a sort of inflammation is obtained, this is only after severe application, but it certainly does not yield anything like a diphtheritic membrane. But on subcutaneous inoculation of guineapigs with diphtheritic membrane, and particularly with cultures of the bacillus diphtheriæ, definite results are obtained which coincide with those described by Löffler, Zarniko, Escherich, Roux and Yersin, and others.

After subcutaneous inoculation with cultures, a few days old, the result is very rapid, and more striking than with diphtheritic membrane; to obtain acute results only a small particle, not more than can be removed from a colony with the point of a platinum wire, often suffices. In the severe cases produced by injecting several minims of a recent broth culture, the animals are very quiet after from twelve or sixteen hours; and a soft painful swelling is found at the seat of inoculation. During the second day the hair is erect, the eyes small, and the temperature is raised; the animals are shaky and refuse food; the condition grows rapidly worse, movement ceases, the body temperature rapidly falls, and the animals are found dead in some thirty to forty hours. In other cases the illness lasts two to three days; in still others as long as five days, or even more. The younger the culture, the more active it is, and the more bacilli are injected, the shorter the illness. On *post-mortem* examination we find hæmorrhage and œdema in and about the place of inoculation, in the subcutaneous and muscular tissues, extending sometimes over considerable areas; when inoculation is made into the groin the changes (hæmorrhage and œdema) extend over the thigh, abdomen, and even chest of the inoculated side; the inguinal glands of the inoculated side are deeply congested. The lungs are more or less congested, sometimes the greater part of one lobe or another is deep purple; pleuritis and pericarditis are often found; the liver is slightly or not at all congested, or is even pale; the spleen is not enlarged; the serous covering of the stomach and intestines is congested; the suprarenals are deep red; the kidney is congested in the medullary part. Neither from the heart's blood nor from the lung, liver, spleen, or kidney can any organisms be cultivated; from the subcutaneous tissue of the inoculated part, particularly from the congested inguinal glands, the writer has obtained the bacilli in pure cultivations, some tubes showing a limited, others an abundant number of colonies; but the culture test is not successful in all animals, though it is in most. Broth cultures (at 35–37° C.) twenty-four to forty-eight hours old, act very virulently, as has been already shown by Roux and Yersin,[1] who have separated certain chemical products from such cultures, and shown that those products themselves act poisonously in proportion to the amounts injected. Roux and Yersin have observed in experimental animals, after inoculation with small doses of broth culture or of the chemical products separated from broth cultures, the same kind of paralysis as occurs also in human diphtheria in the later stages, that is, after the acute symptoms have passed away. While this paper was passing through the press, Dr. Sidney Martin published an account of the chemical nature of the poisons occurring in the human diphtheritic membrane: these same poisonous principles (ferment, organic acid, albumoses) were also obtained from albumen cultures of the diphtheria bacilli. Dr. Martin shows that with some of the chemical products diphtheritic paralysis can be produced, and he further shows that this paralysis is due to degeneration of the peripheral nerves. (Reports of the Medical Officer of the Local Government Board, 1891–1892). Löffler, Roux and Yersin, and others, have concluded that in diphtheria we have to deal with a chemical poisoning, the chemical poison being produced by the living bacilli in the diphtheritic membrane of the human mucous membrane, and in the case of the experimental guineapigs at the seat of inoculation, and absorbed by the system, producing the whole set of general disease symptoms in the lung, liver, kidney, and nervous system, associated with, and characterising diphtheria. The absence of the bacilli from the circulation and all affected organs and their localised presence in the diphtheritic membrane, suggest this. It follows that if the growth and multiplication of the bacilli in the diphtheritic membrane could be prevented or checked sufficiently early—by cautery or otherwise—the amount of the poison would be small, and the disease would cease.

It has been asserted by various authors that a necrotic, chronic, infective process, observed in the mucous membrane of the mouth and pharynx in calves and pigeons, is intimately connected with human diphtheria; but Löffler[2] has shown that this is not the case, since these necrotic processes are altogether different diseases, both as to pathology and as to the microbe.

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[1] *Annales de l'Institut Pasteur*, I.

[2] *Mittheil. aus dem kais. Gesundheitsamte*, vol. ii., p. 482.

Cats, however, have unquestionably been observed[1] to show disease in connection with human diphtheria. In houses where human diphtheria obtained, cats have been known to become ill, either antecedently, or coincidently, or subsequently; they appear to have some kind of throat illness, and cannot swallow; they sneeze and their eyes water; as a rule, bronchial mischief is noticed early, and if the disease is protracted through several weeks, as it sometimes is, they become much emaciated and die. On *post-mortem* examination the lungs are full of grey, consolidated, lobular patches, and the kidneys are always *enlarged and white*; on a section the whole cortex is found to be in a state of fatty degeneration, while the medulla shows congestion. Further, the writer has ascertained that an infectious disease with the same symptoms, and leading to the same result, exists naturally amongst cats; the animals have severe lung trouble, become emaciated, and die with the same pathological appearances, notably on the part of the kidney. In one case the writer has seen such a cat after several weeks' illness showing paresis of the hind extremities.

When cats are inoculated subcutaneously in the groin with a particle of human diphtheritic membrane, they become distinctly ill, show after twenty-four hours a painful swelling in the groin, have high temperature, and refuse food. In the severe cases these symptoms increase in intensity during the next few days, and the animals die before the end of the week. On *post-mortem* examination the subcutaneous and muscular tissues at and near the seat of inoculation are found to contain hæmorrhage and œdema, and the tissues are separated into layers, which are more or less necrotic. The viscera show much congestion, particularly the lungs, also the serous covering of the stomach and intestine as well as the peritoneum; the kidneys are *large and white*, the medulla congested, while the cortex is more or less uniformly fatty (*see* fig. 137). This condition is more marked the longer the illness; when the animals die in three to four weeks, or later, the condition of the kidney is very striking, and then also the lungs show lobular patches of grey consolidation. Still more striking is the result when a particle of a virulent culture of the bacillus diphtheriæ is subcutaneously inoculated. If a fresh culture—twenty-four to forty-eight hours old—is used, the animals are very ill in twenty-four hours: they are quiet, refuse food, the temperature is raised, and at the seat of inoculation is a painful swelling; some animals die after two, three, or four days, others live to the end of the week. On *post-mortem* examination the same appearances of the viscera, notably of the lungs and kidney, are found; and here also the fatty white kidney and the pneumonia are the more marked the longer the duration of the disease; in animals that die forty-eight to seventy-two hours after inoculation with culture, the subcutaneous and muscular tissues about the seat of inoculation show much hæmorrhage, in many parts the tissues are almost gangrenous. When using recent broth cultures derived from the congested inguinal lymph gland of an experimental guineapig (*see* above) the effect of the subcutaneous inoculation of such culture in the cat is most striking; all animals die within forty-eight to fifty hours. In many instances after subcutaneous inoculation, on the death of the animal, the bacillus diphtheriæ has been recovered by cultivation in numerous colonies, but no bacilli can be demonstrated in the lungs, liver, or kidney.

The only animal in which, either with diphtheritic membrane or with cultures of the bacillus, it was possible to produce a definite and striking result on the cornea and conjunctiva, is the cat. If from the cornea and conjunctiva the superficial epithelium is scraped off, and then on such a surface a piece of diphtheritic membrane or a particle of an artificial culture of the bacillus is rubbed in, the result is in most instances positive; after twenty-four hours the conjunctiva looks injected, and the eye watery; after forty-eight hours the animal is quiet, and has the eye closed with much muco-purulent discharge from the inner angle of the eye; the conjunctiva is much congested, swollen, and œdematous; the cornea is opaque, and covered with a muco-purulent film; the condition gradually increases in intensity from day to day, so that by the end of the week the cornea shows a distinct ulcer, crater-like, its margin swollen and opaque. In severe cases the process gradually increases till the end of the third week, when the ulceration of the central part of the cornea reaches the lamina Descemeti; after this time the disease gradually abates, and recovery takes place. In two cases perforation of the cornea took place and purulent panophthalmitis set in. In other cases the duration of the disease is shorter and the process is not so intense. That we have here to deal with a specific infectious disease, is proved by the fact that matter scraped from the ulcerated cornea and transferred to the cornea and conjunctiva of a fresh cat produces again the same specific disease. Ordinary purulent matter applied to a scraped cornea or conjunctiva does not produce any result; after twenty-four hours the conjunctiva is found injected, and the eye watery, but after forty-eight hours nothing abnormal is to be noticed. From the opaque tissue bordering the ulcer in the cornea of the above successful cases the writer has succeeded in obtaining cultures of the bacillus, on gelatine, in numerous colonies; the cultural characters of the colonies were identical with those of the human diphtheritic membranes, but the bacilli themselves were conspicuously smaller in size, shorter and thinner (*see* fig. 78). Also by scraping the mucous membrane of the palate and fauces of the cat, and then rubbing in a particle of diphtheritic membrane, or of a culture of the bacillus, an ulcerative process is produced which reaches its height by the end of the first week, or earlier; the ulcer is surrounded by swollen congested mucous membrane, and is covered with a grey pyogenic membrane.

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[1] Dr. George Turner, Dr. Bruce Low, Dr. C. T. Renshaw, Dr. A. Downes, Dr. Thursfield; *see* the writer's Report in the Volume of the Medical Officer of the Local Government Board, 1889, p. 162.

On account of the above very definite results obtained in the cat with diphtheritic membrane, or with cultures of the bacillus (subcutaneously or on the cornea), and of the peculiar disease of the lung and particularly the kidney, observed in the cat (experimentally or naturally) in connection with human diphtheria, the writer holds that the disease occurring naturally in this animal is equivalent to human diphtheria, and that therefore the cat must be considered as susceptible to human diphtheria, and capable of communicating the disease to other cats and also to human beings.

The important question that must be asked in connection with this assumption is this: Since in the natural disease in the cat there is no diphtheritic membrane to be found in the fauces, how is it possible for a cat to communicate diphtheria to human beings? Such has unquestionably taken place in several instances (*see* Reports of the Medical Officer of the Local Government Board, 1889–1890). A cat in the subcutaneous tissue of which, by inoculation of a particle of diphtheritic membrane, or of an artificial culture, local œdema, hæmorrhage, and necrosis are established at and about the seat of inoculation, contains in the local tumour the bacillus diphtheriæ; and it is here, just as in the case of the guineapig after subcutaneous inoculation, that in consequence of the growth and multiplication of the bacilli the chemical poison is produced which, absorbed by the system, sets up the disease of the viscera mentioned above. Neither in these experimental cats, nor guineapigs, could the diphtheria bacilli be demonstrated in the diseased viscera or the blood of the circulation ; neither in the case of the ulcer of the cornea and the conjunctivitis produced by inoculation into these tissues with human diphtheritic membrane or artificial culture could the diphtheria bacillus be demonstrated in the viscera. And the same we have seen to hold good for human diphtheritic process, i.e. the disease is in the first place a local one, and owing to the elaboration at that locality by the growing and multiplying diphtheria bacilli of certain chemical poisons is the general visceral disease established. But the important question is, Which is that primary locality in the cat affected with the natural disease in which the diphtheria bacilli grow and multiply and produce the chemical poison? From the fact that the animals early show lung disease and bronchitis, leading to broncho-pneumonia, and frcm the fact that the disease is communicated by them to other cats and to children (generally the children have been fondling and nursing the animals) we may, I think, justly conclude that the lungs are the locality which in the natural disease harbour the bacilli. In examining sections thrcugh the diseased portion of the lung of a cat affected with the natural disease, a condition is found to obtain in the large and small bronchi and in the infundibula, vividly recalling the diphtheritic membrane of the human subject; the bronchial mucous membrane is swollen and completely changed into a necrotic, reticulated mass in which the outlines of blood-vessels, distended by and filled with stagnated blood, and a few nuclei are recognisable, the cavity of the bronchi and infundibula being distended and filled with that diphtheritic mass. The writer has in two instances had an opportunity of examining the diseased lung of early cases, the animals dying a few days after they were seized with the illness. In these cases the presence of the diphtheria bacilli in considerable numbers could be demonstrated in the exudation filling the bronchi and infundibula in some of the lobules. But also indirectly he has been able to show that the lung in the cat is most probably the primary locality in which the diphtheria bacillus produces diphtheria, and where it elaborates the chemical poison. Of broth culture of the diphtheria bacillus forty-eight hours old a small quantity ($\frac{1}{2}$–1 c.c.) was directly introduced into the cavity of the trachea without injuring the mucous membrane. The effect of this injection was most striking. Before twenty-four hours had elapsed the animals were found very ill; in one instance death took place in thirty hours. On *post-mortem* examination the lungs were found greatly congested, and there was also hæmorrhage; so also in the liver, the peritoneum, and the kidney. In the bronchial tubes there was much sanguineous exudation; and in this the diphtheria bacilli could be demonstrated in large numbers. In another case the animal lived till the sixth day; it did not feed, got thin, coughed a good deal, and appeared paralysed in one hind extremity. On *post-mortem* examination the whole middle lobe of one lung was found consolidated, was full of blood, and sank in water. On section through this consolidated part, the bronchi and infundibula and also air cells were distended by, and filled completely with an exact counterpart of diphtheritic membrane; also the exudation in the bronchi contained the diphtheria bacilli in smaller or larger clumps. Both kidneys in this case were greatly enlarged and white; in section the medulla was congested, but the entire cortex was white and in a complete state of fatty degeneration. From these experiments the conclusion is justified that, in cats, diphtheria in the lung is possible, and that most probably also in the natural disease affecting the cat, the primary diphtheritic locality is in the lung.

As is well established, diphtheria is a highly contagious disease, transmissible from person to person, its contagium belonging to the group called fixed contagia. But it is likewise well established that milk infected from a human source has, in several epidemics, been the means of producing diphtheria in the consumers. It is also known that a room in which a diphtheria case has once existed may for years harbour the contagium of diphtheria, so that any new-comer or inhabitant may contract the disease; moreover, it is known that in a locality in which diphtheria has once been rife, the disease may at any time reappear, and in these instances the transmission of the contagium from sewers is maintained by some sanitarians. Lastly, it has been shown by Mr. Power, Dr. Mason, and Dr. Philpott, that in certain epidemics of diphtheria (Yorktown and Camberley, Barking, Croydon), while the milk was the vehicle of infection, the milk did not receive its infective power from a human source.

Several epidemics of milk diphtheria, in which fouling of the milk with human diphtheritic material could not be demonstrated, but, on the other hand, could be excluded, have of late years become known, and in these cases the suspicion attached itself to the cows, for it could be shown that there existed on the farms concerned no other condition which in any way could account for the infectivity of the milk; besides, this infectivity was inherent to the milk over a certain period. In the case of the Yorktown and Camberley epidemic (*see* Mr. Power's Report in the volume of the Medical Officer of the Local Government Board for 1886), the cows were certified by a veterinary surgeon to have been in good health, though even several days after the human diphtheria cases had ceased to occur, two of the cows showed some slight signs of 'chaps' on their teats. Mr. Power saw at the farm one cow which had suffered from chapped teats in October 1886 (the month in which the epidemic occurred), and which still had at the beginning of November a scab or crust at the site of a 'chap.' At Barking the cows whose milk produced the diphtheria (in 1888) suffered from a distinctly contagious eruptive disease on the teats and udder, showing itself in sores covered with brown black crusts. The same was noticed in connection with an outbreak of diphtheria (through milk) at Croydon in November 1890. The question which was therefore considered important to decide was this: Can cows be infected with the bacillus diphtheriæ? During the early part of 1890 and 1891 the writer made experiments on milch cows (which had calved some weeks previously), which strikingly showed that this is really the case. The results of these experiments are so definite and so important in connection with milk derived from such cows being charged with the diphtheria contagium, that the writer may be excused for giving two of these experiments somewhat in detail.[1]

A broth culture was made of the bacillus diphtheriæ derived from a human diphtheritic membrane, but passed through several gelatine subcultures; the broth culture had been growing for a few days at 37° C.

One cubic centimetre of the culture was injected under the skin into the subcutaneous tissue of the left shoulder in each of two cows. These animals were, at the time of the experiment, in very fine condition (teats and udder quite clean, copious milk secretion), and had been so during eight to ten days, during which they had been under observation. During the second and third days after inoculation, the body temperature showed a slight rise (to 40°·6), and they did not feed well on those two days; but afterwards the temperature went down to the normal state, and the animals recovered. But at the seat of the inoculation there was a painful, large soft tumour to be felt and seen. On the fifth to the sixth day, for the first time, there was noticed on the udder and on one teat in one cow an eruption of about half a dozen firm papules: red and injected, projecting above the surface of the skin, the subcutaneous tissue indurated with a nodule. In addition to the papules about half a dozen vesicles and two round patches covered with brown crusts could be seen on the udder. Some of the vesicles contained clear lymph, others were pustular, i.e. purulent. On the seventh day new papules and vesicles were found; those of the previous day had already become changed into dark brown crusts. On the eighth day a new crop of vesicles could be noticed on this cow's udder, and on that day for the first time about half a dozen were also seen on the udder of the second cow. In fig. 136 the condition is accurately represented: some are vesicular, others pustular, and still others covered with brown black crusts; the vesicles and pustules were round and prominent, with a narrow margin of injected skin, the crusted places irregular. The whole thickness of the skin and subcutaneous tissue felt hard and nodular. For two or three days (ninth to twelfth day) this went on in the first cow; that is, new vesicles appeared: those that were vesicles with clear lymph one day were pustular the next, and crusted the following day. The crusts did not remain long; after two or three days they became loose, and left a dry healing sore behind, which when recent, on removal, showed a bleeding sore of the corium underneath.

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[1] Report of the Medical Officer of the Local Government Board for 1889, p. 168.

We have, then, here a new eruptive disease on the teats and udder of the cow: a disease marked by papule, vesicle, pustule, sore, and crust, but of a very rapid progress, since the crusts fell off and the sore healed in less than seven to nine days since its first appearance, the skin being at the same time much indurated. This eruptive disease on the udder, be it well observed, was produced by inoculating the animals subcutaneously in the region of the left shoulder with a culture of the bacillus diphtheriæ.

As stated above, in both animals on the second and third days there was a painful, soft tumour to be felt at the seat of inoculation. From day to day the tumour became larger; about the end of the week it was as large as a man's fist; after this time it gradually became firm; but about the fifth and sixth days it was still soft, felt like œdema, and on pressure a quantity of clear serum could be squeezed out from it. After the death of the animals (one died after a fortnight, the other was killed on the twenty-fifth day) the tumour was examined, and it was found to be located in the subcutaneous tissue, but was firmly connected both to the skin above and the muscular tissue below, and was surrounded by œdematous tissue. It presented white streaks, was firm, but on section clear serum could be pressed out from it. Under the microscope the tissue of the tumour was of the same nature as diphtheritic material; a general matrix of reticulated necrotic tissue in which remnants of nuclei, outlines of blood-vessels, and remnants of extravasated blood could be recognised: this tissue shaded gradually both into the cutis and into the surrounding muscles.

Both animals showed normal temperature to the end, but they both coughed and gradually ceased feeding, and did not take any water: one of them by the end of the fortnight suddenly became worse: it took no food or water, its milk failed, its evacuations became scanty and dry, its breathing became very rapid, and after a sudden collapse it died. The other animal twenty-four days after inoculation grew much worse, and was therefore killed.

In both animals the lymph glands nearest the left shoulder, i.e. close to the tumour, were much enlarged, very œdematous, and contained hæmorrhage;

no change in the organs of the throat; both lungs showed extensive congestion, in fact, almost amounting to red hepatisation of the upper lobes and the upper portion of the middle lobe, petechiæ, and hæmorrhagic patches under the pleura; the pleural lymphatics everywhere in the congested portions were conspicuous and distended, either with clear lymph or, as was the case in the second cow, tinged with blood. On cutting into the congested portions the lung was seen to be highly œdematous, a large quantity of blood-tinged serum flowing from, and accumulating at the cut end; the lobules were well mapped out, and there was also sharp demarcation by œdematous connective tissue between the normal lung tissue and the deeply congested lobules, as also between groups of lobules and individual lobules in the congested areas; there were hæmorrhagic spots and patches on the parietal and visceral pericardium. The liver showed yellow-grey necrotic patches, the spleen grey necrotic streaks in the capsule; both kidneys showed congestion of the medulla, and fatty patches in the cortex. We have, then, in both these animals a striking result, completely coinciding with the disease in the cat.

The next important point ascertained in these cows had reference to the distribution of the diphtheria bacilli inoculated. In the tissue of the tumour of both animals after death, i.e. after fourteen and twenty-four days respectively, the diphtheria bacilli could be demonstrated without any difficulty under the microscope in the sections, and by culture. On sections the necrotic tissue of the tumour contained large numbers of the bacilli in clumps; culture experiments on gelatine and on agar with a particle of the tissue of the firm tumour produced innumerable colonies of the diphtheria bacillus; when examined under the microscope they resembled the human diphtheria bacillus in all respects (fig. 77). They were also tested on guineapigs and found to act extremely virulently, causing death of the animals with typical appearances in thirty to fifty hours. But neither in the heart's blood, nor in the lung or liver of these cows, could any microbes be demonstrated in microscopic specimens or by culture. So far, then, there is complete analogy between the cows, guineapigs, and cats, that is to say, the diphtheria bacilli introduced into the subcutaneous tissue produce here by growth and multiplication the chemical poison, setting up the general disease in the viscera. But it will be asked, Is the remarkable eruption on the udder of the cows also a result of the absorption of the chemical poison produced at the seat of inoculation (subcutaneous tissue of the left shoulder)? The nature and progress of the eruption, it must be admitted, had all the characters of what one would be inclined *à priori* to consider under other conditions as an infectious process; and if so, it most probably is not merely a symptom of the work of the chemical poison, though it might be, since, for instance, in certain chemical poisonings, e.g. in bromide, a 'bromide rash' in the skin, even resembling vaccinia to a certain extent, is well known. That in these cows the eruption was not of this nature was directly proved by inoculating, into the subcutaneous incisions in the groin and abdomen of calves, matter taken from the eruption of the cows in the vesicular and pustular stages. The result of this inoculation was that the typical eruption of the cow was reproduced, though its appearance in the calves was somewhat delayed.

But the presence of the diphtheria bacillus in the eruption of the cow could be demonstrated both microscopically and by culture during the vesicular and pustular stages; in the latter also numerous pus cocci.

That in the cow the diphtheria bacillus as such passed into the system of the animal and appeared, not in the viscera, but on the udder, was demonstrated conclusively by the fact that before the end of five days after inoculation, the presence of the diphtheria bacillus could with certainty by microscopic and culture observations be demonstrated in the milk of the cow collected under all precautions; the number of bacilli present on that day in the milk amounted to thirty-two per cubic centimetre.[1] It need hardly be added that these results lead in great measure to a right understanding of certain epidemics of milk diphtheria, such as those of Camberley and Yorktown, Enfield, Barking, and Croydon.

Von Emmerich isolated short thick rods from diphtheritic membranes, with which he produced a fatal disease in pigeons, rabbits, and mice. He found that, inoculated into the mucous membrane of the trachea of rabbits, the microbe caused death in sixty hours, with grey fibrinous membranes on the mucous membrane; the bacilli were present in the mucous membrane, blood, and viscera.

Löffler[2] showed that the so-called diphtheritic deposits in the mucous membrane of the fauces, larynx, and conjunctiva of fowls and pigeons are not the same as those of human diphtheria; in the pigeon it is different from that of fowls, while in the former it is caused by minute bacilli, thinner and a little longer than those of rabbit's septicæmia (Davaine, Koch); he also showed that the so-called diphtheria of calves is not the same as human diphtheria, since it is caused by long bacillary threads. Lingard and Batt had previously found the same bacilli in the necrotic masses in the mouth in calves; they have described the disease as a chronic ulcerative necrotic stomatitis. Dr. Lingard has shown that it is transmissible to the rabbit's ear, wherein the characteristic bacilli produce the same chronic necrotic ulcerative process.

As to the necrotic deposits in the fauces and mouth of fowls, not at all rare amongst poultry, and regarded by some as identical with human diphtheria, Löffler has pointed out that it is different from the similar disease in the pigeon; it certainly is not due to the same bacteria as those shown by Löffler to be the cause of the pigeon's disease. The writer has cultivated from the caseous yellow white deposits in the pharynx and mouth of such a fowl an organism which was present in almost pure culture. The yellow-white deposits are dry and brittle, and are made up of epithelial cells and *débris*. There are present various species of microbes in the superficial layers; but in the deeper parts one species of minute more or less constricted rods predominates, of the same size as those of fowl cholera, but differing from these latter by the fact that on potato they form rapidly a characteristic deep yellow growth; on gelatine, even after twenty-four to forty-eight hours they form white, round, prominent dots, which become more yellowish and project over the surface like little buttons, and are easily lifted off bodily; they are very tenacious, and do not break up when shaken in fluid.

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[1] During 1890–91 the writer repeated these experiments on milch cows, and in two further instances out of six cows the eruption was produced on the udder and teats; in one of these positive cases the milk contained the diphtheria bacillus at about the end of the first week after inoculation (subcutaneously into the shoulder) with culture of the bacillus diphtheriæ.

[2] *Mittheil. aus dem kais. Gesundheitsamte*, vol. ii.

SECTION C

CHAPTER XX

FEVERS

TYPHOID OR ENTERIC FEVER

THE most prominent pathological changes characteristic of this and of no other disease are those affecting the Peyer's glands of the ileum, the mesenteric glands, and the spleen.

(*a*) *The Peyer's Glands.*—These show in the earliest stages—i.e. during the first week of the disease—a conspicuous increase in size, due to multiplication and enlargement of the cells of the lymph follicles, and to exudation of plasma into the latter; hence they are also more juicy. The mucosa and the sub-mucous tissue around and between the follicles of the Peyer's glands are much infiltrated, swollen, and the blood-vessels congested; and so, in a conspicuous degree, are the vessels of the lymph follicles constituting a Peyer's gland and of the parts immediately surrounding it—*stage of infiltration.* When the enlargement of the lymph follicles reaches its maximum the centre part undergoes a necrotic change—coagulation necrosis—the blood-vessels here being found in a state of hyaline degeneration; under the microscope one finds a network of coagulated fibrin threads, many lymph cells, which are enlarged, opaque and not taking dyes; in some the nucleus is faded and indistinct and not easily distinguishable, others breaking down into granular *débris.* This second stage, or *stage of coagulation necrosis*, extends in all directions till all parts of the Peyer's patch, particularly towards the internal surface, have become necrosed; the deeper parts, i.e. those situated in the sub-mucous tissue, as well as the latter, remain actively inflamed, their lymphatics being filled with coagulated fibrin and the connective tissue more or less infiltrated with lymph cells. During the second week the necrosed part being in a state of granular *débris* gradually breaks away, and thus an ulcer is established—*stage of ulceration.* The ulcerated Peyer's patch is crater-like, and is surrounded by a thickened, swollen, densely infiltrated mucosa, whose lymph cells are greatly enlarged; the base of the ulcer is the deep, sub-mucous portion of the Peyer's gland, while its surface is covered with granular *débris*, the remains of the necrosed part of the Peyer's patch. The ulcer, that is, the necrosis, enlarges (third week) in breadth at the expense of the mucosa immediately surrounding the original Peyer's patch, and in depth at the expense of the sub-mucous tissue and the circular muscular coat; but the reactive inflammation in the depth is, as a rule, a barrier and causes a gradual removal of the necrosed *débris*, and then the healing process commences (fourth week). In this process the place of the original Peyer's gland is transformed into a depressed pigmented scar, limited towards the depth by the outer layer of the muscular coat. During the increase of the inflammation and ulceration into the depth, i.e. into the outer muscular coat, the process may lead to perforation; the ulceration into the depth may also involve one of the larger vascular trunks of the sub-mucous tissue, and thus produce hæmorrhage.

The cicatrix which after healing occupies the place of the original Peyer's gland is easily detectable as a pigmented depression.

(*b*) *The Mesenteric Glands.*—The mesenteric glands show changes of the same kind as those of the Peyer's glands already mentioned; but no ulceration takes place here. During the first week the glands are considerably swollen, very juicy, and much congested. In a section it is noticed that the gland contains a good deal of fluid; under the microscope it is seen that the lymph follicles of the cortex, particularly their central parts, are filled with fibrinous exudation, that the lymph cells are enlarged, and some contain many nuclei; in the sinuses, both cortical and medullary, the cells of the reticulum filling the sinuses are also much swollen and very conspicuous. The lymph glands continue to increase in size and juiciness till the third week. During the second week, there are found, as in the lymph follicles of the Peyer's glands, numerous spots and patches, in which coagulation necrosis has occurred. These necrosed patches gradually increase in size till the end of the third week; the lymph cells and fibrin networks constituting these necrotic patches undergo granular disintegration and fatty metamorphosis, and in this condition gradually become absorbed and disappear. There are present in the lymphatic tissue, in all parts of the gland and at all times, lymph cells which are conspicuous by their size, spherical in shape, and several times as large as the largest normal cells: they contain either one large nucleus or several smaller nuclei, their substance being filled either with coarse granules, or vacuoles, and at times also with blood-discs.

(*c*) The spleen is always enlarged, and this is chiefly due to an enlargement of all blood spaces and of the lymphatic tissue, i.e. the Malpighian corpuscles. As to the former the blood spaces of the pulp are considerably distended and filled with blood, and the cells constituting the pulp are enlarged; in some places all the pulp cells are changed into large spherical corpuscles containing blood-discs, being occasionally crammed full with them. In the enlarged Malpighian corpuscles the central parts also undergo the necrotic change described above, and these patches gradually increase in size, involving the surrounding pulp tissue to a greater or lesser extent. At the same time necrosed patches are found independently in the pulp, and are due directly to infarct in the pulp; such infarcts, and consequent necrosis, may produce extensive necrosis of the pulp tissue. The large cells filled with blood-discs above named are always present in the pulp from the earliest stages, and are occasionally washed into the circulation, and can then be met with also in the circulating blood.

Other changes in typhoid fever occurring at later stages must be considered as sequelæ, and due to secondary causes: thus the pneumonia is due to an infection with microbes capable of producing pneumonia. The diplococcus pneumoniæ, streptococcus pyogenes, and Friedländer's bacillus have been isolated from such pneumonias. The granular and fatty degeneration observed in the liver cells must also be considered as due to secondary causes, perhaps chiefly the high temperature; the waxy degeneration of striped muscular tissue of Zenker is probably due to the same causes. Necrotic patches in the liver and spleen pulp—the infarct above mentioned—the necrosis and suppurations occurring as sequelæ in various tissues are probably due to a secondary invasion with pyogenic cocci or similar microbes. In the necrotic patches in the spleen, clumps of micrococci are almost constantly met with.

On the whole, then, we may say that the swelling and coagulation necrosis observed in the lymph follicles of the Peyer's gland, mesenteric glands, and the tissue of the spleen are the primary lesions, and in the intestine the necrosis leads to the formation of open ulcers.

Etiology.—Since the clear and precise statements by Budd in his well-known memoir on typhoid fever, this disease has been considered to be disseminated by the stools of a previous case of typhoid fever. That in this dissemination water plays an important part has long been accepted, and one might almost say has been all but proved. Various epidemics and groups of cases have been investigated, both in this country and abroad, where a contamination of drinking water by sewage (old cesspools and drains), and by inference with typhoid excretion, had been proved to be connected with the outbreak and the spread of the disease. Von Pettenkofer, no doubt, showed for Munich that in the dissemination of typhoid the state of the ground water plays an important part, inasmuch as after a fall of this, leaving behind in the superficial layers of the soil the germs of the disease, the outbreak and spread of typhoid are caused and favoured, while on the rise of the ground water these poisonous particles again become submerged and prevented from escaping, and hence a subsidence of typhoid fever cases. But this ground-water theory, though applicable to Munich, has not been found to explain the rise and fall of typhoid fever in other localities during other epidemics, and therefore other conditions, notably, those of contamination of water or food stuffs with matter directly derived from sewage, and indirectly from bowel evacuations of typhoid fever cases, had to be considered. Further, Ballard has shown that in the dissemination of the virus of typhoid fever, as in the Islington epidemic, milk plays an important *rôle* ; such milk typhoid epidemics, where the milk had directly, or by the vessels containing the milk, been brought in contact with sewage-polluted water, have since been abundantly recorded, as proved by an inspection of the tables collected for the 'Transactions of the International Medical Congress,' London, 1881.

The most complete and instructive evidence as to contamination of drinking-water by typhoid stools, and wholesale infection by such drinking-water, was brought forward by Dr. Thorne Thorne in elucidating the now famous epidemic of typhoid fever in and about Caterham. This report for 1878, published in the volume of the Medical Officer of the Local Government Board, contains the full account on this most instructive and now classical piece of epidemiological work. It was proved that one of the *employés* at the Caterham works of the Kent Water Company, while actually affected with typhoid fever, managed to contaminate with his stools the water at the original wells of the company, and this contaminated drinking-water, in its distribution about Caterham, Reigate, and other places, produced in the consumers typhoid fever.

The next important question that requires to be answered is, What is there in the stools which must be regarded as the virus of typhoid fever ? This virus must be a microbe which evidently can live and thrive in sewage and in the soil ; further, that it can retain vitality even when placed in such a poor medium as water ; it must be possessed of considerable resistance towards putrefaction, towards cold, and towards the gastric juice ; when brought, in the stools of a typhoid fever case, into drains, cesspools, and the like, it must be capable of preserving its life for an indefinite time—all these are requirements postulated by what is known of the epidemiological relations of typhoid fever. Many sanitarians have formulated these general conditions into a single sentence by saying that the typhoid-fever microbe must be capable of forming spores, and by these overcome all the above difficulties, since it is known that a microbe having formed spores can under favourable conditions preserve vitality till the suitable moment arrives, e.g. when finding entrance into a new individual ; the spores are capable of withstanding all kinds of unfavourable conditions of environment, e.g. cold, putrefaction, paucity of nutriment, and struggle with other less specialised microbes, &c. Numerous have been the assertions of the occurrence of micrococci in the intestine, the mesenteric glands, and the spleen in typhoid fever, but only during late years, since exact methods of staining and cultivation have been employed, has a definite species been shown to exist in the typhoid stools in the diseased intestinal mucous membrane, in the mesenteric glands, and in the spleen, occasionally also in metastatic foci of other organs: liver, lungs, brain, and kidney. Eberth first showed that in many cases of typhoid fever there occur in the swollen mesenteric glands, peculiar bacilli rounded at their ends, and occasionally including within a pale sheath one or more spore-like granules. Gaffky[1] may justly be said to have first successfully isolated and cultivated these bacilli of Eberth. Gaffky easily demonstrated them by cultivation from the typhoid stools, from the contents of the ulcerated Peyer's glands, from the swollen mesenteric glands, and particularly from the swollen spleen. In sections he demonstrated them in large and small clusters, in the swollen or already ulcerated Peyer's glands, in the swollen mesenteric glands, and in many places in the spleen. Though Gaffky did not succeed in cultivating them from every case, yet from the majority of cases he did succeed. Gaffky showed that the bacilli are always absent from the circulating blood, while from the spleen and the intestinal contents they can be readily isolated by cultivation and by staining cover-glass specimens. Numerous observers have confirmed these statements, and these bacilli are now, by many, if not most pathologists, considered as the microbes or bacilli of typhoid fever. They are also known as Gaffky's bacilli; the individual bacilli are cylindrical rods or filaments of various lengths, possessed in the fresh state of active locomotion: the short ones move briskly, the longer cylindrical rods or filaments showing a peculiar, slow, serpent-like movement. The bacilli grow well at 16–20° C. on and in gelatine, better of course at 25–37° C., e.g. in alkaline broth, on agar, in gelatine, on blood serum. On boiled potato at 35–37° C., they grow in a fairly characteristic manner, forming on it a transparent thin pellicle, whose thickness increases as the growth proceeds.

On the surface of gelatine they form colonies visible after thirty-six hours as translucent round dots, which during the third and fourth days become flat, translucent plaques with crenate outline; under the microscope they are brownish in transmitted light and granular; in streak cultivation the line of inoculation becomes marked after two to three days as a greyish translucent band, with uneven, knobbed or crenate outline; in stab culture the stab after a few days is seen as a grey line under the microscope, and in transmitted light it is made up of light brownish droplets; on the surface of the stab is a crenate, thin grey plaque. On agar they form a rapidly growing paint-like, cohesive, greyish-white to light brown pellicle; broth is made uniformly turbid after forty-eight hours; a greyish, powdery, or floccular precipitate, no distinct pellicle being formed. The bacilli are facultatively aërobic, but the character of the bacilli in and on gelatine, agar, or broth is not sufficiently marked to distinguish these bacilli from many others, but taking their appearance in the fresh state and in cultures on potato, together with the appearances on other media, the diagnosis can be made without much difficulty.

Typhoid fever has not been communicated by any experimenter to the lower animals; although septic, toxic, and septicæmic results have been produced in rodents by injection of typhoid fever stools and typhoid matter, there is no record of any result that can be at all interpreted as typhoid fever. Not even in monkeys has the writer been able to produce positive results by feeding them copiously on typhoid stools. Fränkel and Simmons, injecting rabbits with considerable quantities of cultures of the Gaffky bacillus, produced death in a day or two under symptoms and pathological appearances which were considered by those observers to be indicative of typhoid fever, but which all pathologists now consider as due to septic infection. Sirotinin, Beumer, and Peiper[1] have shown that the broth in which the bacillus had been growing, injected after the removal of the bacilli, produces, according to the quantity used, severe septic intoxication and even death; further: animals (mice) injected with such a quantity of the broth culture as will produce illness, but not death, are thereby protected against a (second) fatal dose. But in these respects the toxic character of the broth cultures and the protective influence of small quantities of such cultures against a (second) fatal dose is equally true of a number of other microbes, as has been shown by numerous observers (Löwenthal, Roux and Chamberland, Roux and Yersin, Beumer and Peiper, Salmon, and many others).

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[1] *Mittheil. aus dem kais. Gesundheitsamte*, vol. ii., p. 372.

White mice are in a large percentage of cases very susceptible to the pathogenic action of the cultures of Gaffky's bacillus; the majority of the mice inoculated with a small particle of a culture under the skin of the back die in one to three days with symptoms of septicæmia; the blood of the general circulation and the enlarged spleen containing the bacilli in great crowds, and pure cultures on gelatine can easily be obtained from these tissues.

The writer has met with bacilli in the swollen mesenteric glands of a child dead with the symptoms of acute summer diarrhœa, which microbes were isolated and cultivated, and whose cultures, and cover-glass specimens of such cultures, showed a remarkable similarity to Gaffky's bacilli. In plate cultivation, in streak and stab cultures, in broth and on potato, no distinction was possible between the two; in fresh specimens, and in stained cover-glass specimens, the bacilli appeared to be the same; when cultures were injected under the skin of mice exactly the same septicæmia, with crowds of bacilli in the blood of the general circulation and in the swollen spleen, was the result. After a long investigation, a difference was found between the two species; it is this: the bacillus of typhoid fever possesses a markedly lower resisting power to perchloride of mercury than the bacillus obtained from that case of summer diarrhœa; the latter grows fairly well, though retarded, on gelatine to which perchloride of mercury is added in the proportion of 1 in 40,000, while such addition has a much more marked restraining power on the typhoid bacillus.

Eberth, Gaffky, and others maintained that the typhoid bacillus is capable of forming spores; in potato cultures the bacilli constantly show bright terminal globules which Gaffky interpreted as spores; but Buchner has conclusively shown that these globules are, morphologically, not to be regarded as spores, that they are to be seen only in potato cultures, and are not identical with vacuoles also present, but that they represent involution products. Both Wiltschoud and Schiller ('Arb. aus d. k. Gesundheitsamte,' V.) concur in this view. The drying of a thin layer of the culture of this bacillus —no matter of what age the culture, and no matter what the medium and whether grown on the surface or in the depth—kills the microbe, and in this respect there is a striking difference between real spore-bearing bacilli and the typhoid bacillus. The writer has convinced himself also of the fact that the typhoid bacillus never survives a temperature of 60° C. for five minutes, and in this respect too it behaves in a manner totally different from spore-bearing bacilli.

As must appear from the foregoing, the difficulties in accepting as satisfactory the evidence concerning the etiological importance of the Eberth-

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[1] *Zeitschrift f. Hygiene*, Band I., p. 489.

Gaffky bacillus are neither few nor small: (*a*) the bacilli are not constant in every case of typhoid fever; (*b*) they are not present in the blood; (*c*) they occur in tissues (intestinal wall, mesenteric glands, spleen) in which owing to the nature of the disease serious disorganisation occurs, and therefore a secondary immigration of microbes from the cavity of the intestine is hereby much favoured and facilitated, particularly if it be remembered that the occurrence of the bacilli in these tissues has, for obvious reasons, not been demonstrated before the second or third week; (*d*) the bacilli do not form spores; and lastly, but not least, (*e*) domestic animals are not susceptible to typhoid fever, and therefore the crucial argument cannot be furnished.

That in typhoid fever this particular species should abundantly occur—they are never numerous in the stools, and if they appear they are not to be demonstrated before the eighth day of illness (Wiltschoud, St. Petersburg, 1887)—but not in other states, may only mean that the pathological conditions of the intestine in typhoid fever, being peculiar and *sui generis*, favour the growth and multiplication of this particular species of bacilli more than others. It is, however, by no means certain that, as was once believed, these bacilli occur only in the stools of typhoid fever; the results of recent observations seem to point to the conclusion that the bacterium coli commune of Escherich, which is a microbe present in the normal contents of the large intestine, is so similar in morphological, cultural, and physiological respects to the typhoid bacillus, that many observers cannot distinguish the one from the other (Arloing, Roux and Rodet, Congress of Hygiene, 1891). But we must be clearly understood that we do not deny that the Eberth-Gaffky bacillus may be the microbe of typhoid fever; we only wish to point out that anything like good and satisfactory evidence in this respect is not forthcoming, though many take it for granted that it has been proved that this bacillus is the cause of typhoid fever, and even pretend to be able to diagnose from the presence of this bacillus in water and other materials that such water and other materials have been and are capable of being the cause of typhoid fever. The utmost that in such cases can be said is that possibly, perhaps probably, such water and other material has been contaminated with excremental matter. In connection with this the conclusions arrived at by Lehmann as to the uncertainty of identifying the typhoid bacillus outside the body ought to be remembered; by Babes,[1] as to nineteen different varieties of typhoid bacilli found in the bodies of patients dead of typhoid fever; and lastly, of Cassedebat,[2] who found in Marseilles drinking water three different kinds of bacilli resembling the typhoid bacillus.

The bacilli of Gaffky when kept in common drinking water, or better still in sterilised water, gradually diminish in numbers; in fact, many die of inanition, as has been proved by numerous observers. In this respect these bacilli do not differ from other non-spore-bearing bacilli.

Malta Fever

Under this term a continuous fever has been described by Dr. Bruce, of Netley (the 'Practitioner'), which occurs in Malta, and until recently was confused with typhoid fever, the symptoms of the disease being similar in both cases, though from Dr. Bruce's careful account the temperature curve in Malta fever differs materially from that in typhoid fever. No typhoid bacilli were found in the spleen in cases of Malta fever. The pathology of the two diseases is also in this respect different, that in Malta fever there is no ulceration of Peyer's glands, so characteristic of typhoid fever. The spleen in Malta fever is usually enlarged. Dr. Bruce invariably found in the swollen spleen of nine cases the same species of micrococcus, which shows the following characters in microscopic specimens and in cultures. Under the microscope the micrococci appear as small oval cocci, measuring about 0·0008–0·001 millimetre, not forming chains. They grow best in agar jelly above 22° C.; at or below this temperature they show no growth, or only very scanty and retarded growth. At 25° C. it takes about seven days before the growth becomes visible to the naked eye; at 35° C., about half the time. In stab cultures in agar jelly, there appears along the track of the needle a row of minute white dots, but on the upper free end of the track a characteristic rosette-shaped group of whitish knobs or patches makes its appearance. There is no tendency to liquefaction of the jelly, and even after the lapse of twenty-one days the growth on the surface is restricted to the original point of starting.

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[1] *Zeitschr. f. Hygiene*, Band IX., p. 2.

[2] *Annales de l'Institut Pasteur*, 1890, No. 10.

Experiments of inoculation of cultures into guineapigs, rabbits, and mice, had no result. But in one monkey subcutaneous inoculation with a culture produced a definite and well-marked result, inasmuch as it set up a severe fever (temperature rising to 105, 106, and even 107° F.), lasting for twenty-one days, when the animal succumbed. The spleen was found enormously enlarged, and from it the characteristic micrococci were easily obtained by culture.

RELAPSING FEVER

The most noteworthy pathological changes in this disease affect the spleen, the marrow of the bones, and the liver (Pomfick). The spleen is enlarged, due to increase in size of the blood spaces in the pulp tissue as well as to an enlargement—inflammatory hypertrophy—of the Malpighian corpuscles; in cases that are the subject of a *post-mortem* examination, the spleen shows infarct, or necrotic patches in a state of breaking down and suppuration. The same applies to the red marrow of bones, which shows the same appearances as the spleen, viz. as a rule, inflammatory hypertrophy, occasionally in severe cases infarct and necrotic patches. In the liver the whole organ seems enlarged, the liver cells almost uniformly swollen, in many lobules opaque and granular; in severe forms there are larger and smaller accumulations of round cells in the interlobular tissue, extending also into the interior of the lobules; at the same time there are places where in and around the central vein of the lobules the vessels are much distended, with blood in stasis, thus forming an infarct; such a part is whitish on naked-eye view, and under the microscope the liver cells are opaque, granular, and show coagulation necrosis.

Obermeyer ('Centralbl. f. d. med. Wiss.,' 1873, No. 10) discovered during the febrile stage, in the circulating blood of patients affected with this fever, innumerable spirilla actively motile: they disappear from the blood immediately before the end of the febrile stage.

The spirilla are very thin and about 20–30–40 μ long; their movement is that of rapidly progressing spirals. Koch has demonstrated by photography of dried and stained specimens the presence of the flagella in the spirilla. Weigert has shown that, unlike other bacteria, they are barren of a cellulose sheath, since dilute liquor potassæ dissolves the whole substance of the spirilla. By drying and staining cover-glass specimens it has been shown that the spirilla are uniform spirals, and do not show anything that might be interpreted as being made up of shorter elements, comma bacilli or vibrios. The spirals when long are often plicated, but their turns are always close, and more or less in the manner of a corkscrew. Immediately preceding the febrile stage they appear in the blood, grow more and more numerous during the fever, and disappear again completely from the circulating blood before the fever quite ceases. During the non-febrile stage they are most probably present in the spleen and marrow of bone—Birch-Hirschfeld found many of them in the necrotic foci of the spleen—where perhaps they undergo germination and reproduction. It is feasible to assume that when during the febrile stage they reach the height of their development they gradually break down, leaving spores in the shape of granules behind: these are carried into the spleen and bone marrow, where they accumulate. During the non-febrile stage these spores germinate here again, and gradually grow into the spirilla, which when ripe and motile gradually find their way again into the blood. Such a view would well harmonise with the facts of the case and also with what has been shown to occur in regard to the plasmodium malariæ. As a matter of fact the spirilla in the blood often show bright granules in their interior which might well be spores.

Koch has shown that in artificial culture the spirilla are capable of growing into long spiral filaments matted together, but no real artificial cultures have been as yet produced. That the spirilla are the real microbes of relapsing fever is proved by the experiments of Vandyke Carter ('British Medical Journal,' October 1881), who was the first to produce typical relapsing fever in the ape after injection of blood of a patient taken during the febrile stage and containing the spirilla. The disease produced in the ape was true relapsing fever, and the animal's blood contained during the febrile stage the identical spirilla in large numbers. Koch, Heydenreich, and Metschnikoff have confirmed this. Motschutkowsky ('Deutsches Archiv f. klin. Med.,' Band XXIV.) has produced relapsing fever in the human subject by inoculation of blood containing the spirilla.

Metschnikoff ('Virchow's Archiv,' Band CIX., 1887) maintains that the final disappearance of the spirilla from the system, i.e. recovery, is due to phagocytes, that is to say, that the white cells of the spleen tissue eat up the spirilla, and thus purge the system of them; but though spirilla are found enclosed within white cells in the disease in the monkey, it does not follow that his view is correct, for Baumgarten has justly pointed out that as in other localities in other diseases so also here in relapsing fever the enclosure of the spirilla by leucocytes may and probably is only a result of the microbes having previously been killed by other agencies; for after this they are easily taken up by the white cells just like other dead formed matter.

CHAPTER XXI

ASIATIC CHOLERA—DYSENTERY

The name 'cholera' is given to a group of acute diseases, which manifest themselves by profuse diarrhœa of more or less fluid evacuations and vomiting. In severe forms there are cramps of the muscles of the lower extremities, pain in the abdomen, coma, and suppression of urine. But the causes and pathology are widely different in the different kinds. There is first of all a form of cholera which almost in all large cities occurs in the summer months as a few sporadic cases: such are called sporadic or English cholera, or cholera nostras. But also at other times of the year cases occur similar to those, and not having any tendency to spread; such cases occurred in the north of London in numbers during the winter months of 1887; further, isolated cases occur which are ascribed to the eating of over-ripe fruit, of tinned meat, of ice cream, of sausages, of pork pies and various other articles. In these cases there is no tendency of the disease to spread; it only attacks those individuals who have been directly subjected to the influence (eating) of the poisonous matter. But there is one form of cholera which has this great and fundamental character, that it rapidly spreads, and thus assumes the proportions of an epidemic. This form is called Asiatic or true cholera. It is endemic in the Delta of the Ganges; whence at particular periods it spreads over other parts of Asia, where its ravages in some years assume terrible proportions. In Europe, Asiatic cholera has repeatedly broken out epidemically, and then the fact that it has been introduced from a previously infected locality (Africa, Asia) has been fully established. Similarly its appearance in America has thus been shown to be due to introduction from an infected locality. It is not our object to consider in detail the epidemiological aspect of this dire malady, but a few points bearing on the subject of the etiology will be mentioned here. First of all the fact that an epidemic of cholera in a given locality outside Asia may, and often does, recur the next year and perhaps the third year, though the intensity of the epidemic and the number of its victims gradually becomes lessened, is proved in almost every one of the several visitations by cholera of European countries (for instance, the cholera that appeared in France in 1884 and 1885, in Italy and Spain in 1885 and 1886). Next as to the way cholera is introduced into a new locality. This has been proved to be either by articles derived from an infected person or an infected district, linen soiled by cholera dejecta, or a person or persons suffering from cholera, moving from one locality to another. In this move persons may—and have been known to have actually done so—give rise to new foci wherever they alight and wherever their discharges (evacuations and vomit) get access to drinking-water or food. Once a person affected with cholera enters a new locality and his discharges find access to a suitable soil, where the virus is capable of multiplying, a number of new foci can be hereby established, each of which in its turn may supply the poison for water and articles of food for considerable areas. Thus it happens that after the discharges of a person affected with cholera have gained access to the soil, where the virus multiplies and spreads and finally finds opportunity to gain access to drinking water, this latter becomes at once the means of producing infection in a large number of persons partaking of such water (*see* Dr. Snow's Report on the famous Broad Street Pump epidemic). Wherever in one way or another the cholera virus is deposited in a suitable soil it multiplies and spreads, and is capable of contaminating articles of food, fruit, milk, or water, and thereby causing infection. A further important etiological point of view is the fact that while the choleraic discharges have been known to be the vehicle of the cholera virus, there are cases on record where the cholera discharges, though copiously present and introduced into certain localities in which all conditions of sanitation were of the worst description—both as to filth, overcrowding, and contamination of water—did not produce infection. That this is the case in India and also in Europe has been repeatedly observed. Thus in India cholera in anything like an epidemic form is observed only during certain seasons of the year, December to July; later than July, or earlier than November, though cases may and do occur, or new cases may be and are introduced into a locality, as a rule no such marked tendency to spread and to assume the epidemic form is noticed. In Europe, April till October are the months in which cholera, when it does occur, assumes an epidemic form; during the winter months cases are scarce, or with the winter months cases cease altogether, to break out again in the next spring (*see* the last cholera epidemics in France, Italy, and Spain).

Further, besides season, locality plays an important part in the spread of cholera. Cholera, as has been so often shown, and as has been so much insisted upon by Sir John Simon in his writings on the spread of infectious disorders, is essentially a filth disease, that is to say, it depends in its introduction and in its spread on filth, this being the ground on which it grows and multiplies luxuriantly, and it is such filth that gives infective power to water and food stuffs. But although what health officers term 'insanitary conditions' play the very first *rôle* in the introduction and spread of cholera, yet there are localities which, notwithstanding their highly insanitary conditions, seem nevertheless unsuitable for the disease taking any strong footing (Lyons, Rome). Such localities possess a certain immunity against cholera, an immunity which has always seemed to offer a serious obstacle to the assumption—almost generally made—that the cholera dejecta *per se* in the fresh condition contain the actual cholera virus. Von Pettenkofer, Dr. Cuningham, the late Sanitary Commissioner to the Government of India, Drs. Lewis and D. D. Cunningham, and many others, who have studied the various outbreaks of cholera in India and Europe, have always insisted on this fact, viz. that unless season and particularly locality are favourable, cholera dejecta, though deposited and introduced in large quantities, do not seem to exert infective properties. It is therefore assumed —to explain this peculiar behaviour of the cholera virus—that the cholera dejecta contain the virus only *in posse*, that this for its 'ripening' requires to be deposited in a suitable soil; that is to say, a soil in which it can live and thrive, and in which it can reach and attain that form in which it becomes infective to those whose alimentary canal it enters. That most cases of cholera are brought about by contaminated water and food, or, to speak generally, by the alimentary canal, is almost a universally admitted axiom, and it would appear that the infective stage of the cholera virus which it attains after sojourning in a suitable soil is something comparable to a spore stage. We shall see later on from other etiological reasons that this is most probably the case, and we shall give several instances in which cholera dejecta, though abundantly introduced in certain localities, did not produce infection.

In Asiatic cholera one of the most conspicuous symptoms is the diarrhœa of thin watery evacuations, associated with vomiting. When a cholera patient succumbs during the first twenty-four to fifty hours of the disease the *post-mortem* appearances are these: In a number of cases the serous covering of the stomach, jejunum, and ileum shows redness, is pale rose-coloured, either patchy or diffuse, with a sticky thin layer of exudation; the same sticky exudation is found on the mesentery; the mucous membrane of the jejunum and ileum, particularly the latter, is tumid and injected; this is especially noticeable in the lower ileum, where here and there deeply congested patches occur in the mucous membrane. The epithelium of the mucous membrane throughout the small intestine is detached in flakes or is only loosely adherent; by placing the opened intestine under water the epithelium is seen to be in the process of detaching itself from the villi in large areas; the small intestine is distended and its cavity contains a more or less colourless, watery fluid in which numerous small or large mucus flakes are suspended. Under the microscope these are made up of a homogeneous mucus basis in which are enclosed epithelial cells of the surface either isolated or more generally in small or large groups; some of these flakes are entirely made up of groups of epithelial cells. These are the cases which, during life, voided large quantities of fluid, watery evacuations—per mouth and rectum—and in which numerous mucus flakes are suspended. Owing to this condition, the evacuations are called rice-water evacuations; these cases are most typical also in other respects, viz. violent symptoms of vomiting and purging of rice-water-like fluid, great fall of temperature in the first stage—stadium algidum, cold extremities, violent and painful cramps in the calves, sunken eyes, ghastly look of face, small hollow voice, suppression of urine.

Not only the small intestine but also the large intestine contains that watery rice-water-like fluid, though in the earlier stages lumps of fæcal matter may be still discerned in the lower parts of the colon. If during life copious rice-water stools have passed off, the large intestine is found *post mortem* to be void of solid fæces. In another set of cases, also ending fatally, during the first day or two, though the contents of the small intestine are fluid, they yet contain coloured, thin, almost fluid fæces, often mixed with blood; in these cases the mucous membrane of the ileum shows petechiæ and hæmorrhagic patches. If death takes place after the first stage or the stadium algidum, i.e. during the typhoid stage, the small intestine contains little of the fluid matter, though the general injection of the mucous membrane is still distinct; in these cases the large intestine contains fæcal matter. The kidneys, spleen, and liver show venous congestion, so do the cord and brain; the pia mater particularly is much injected.

Examining microscopically the intestinal discharges of acute cases of cholera one notices besides detached epithelial cells and mucous corpuscles, numerous bacteria belonging to different species of micrococci and bacilli. Some there are amongst them which are comma-shaped, i.e. curved, cylindrical rods, single or double, or S-shaped; they are motile, spinning round or moving in a spiral; they are of different lengths and of different amount of curvature, but, as cultivation experiments show, all belong to the same species; namely, the comma bacilli, or vibrios or spirilla of Koch, discovered by him as constantly present in the acute stages of Asiatic cholera, and as showing definite cultural characters.[1] There exist, however, considerable differences with regard to the number of these comma bacilli present. In some acute cases with typical rice-water stools the mucus flakes or the intestinal fluid contain these comma bacilli in enormous numbers, almost to the exclusion of other bacteria; such is the case in some typical cases in the mucus flakes taken directly from the watery contents of the ileum, though the mucus flakes taken in the same body from the jejunum, in all other respects identical, contain but few of these comma bacilli. In other equally typical acute cases they are scanty, other bacteria being very numerous. The writer cannot confirm Koch when he says that the more acute, severe, pure and typical a case, i.e. the more the intestine contains only the rice-water fluid with mucus flakes, the more numerous are the comma bacilli in the contents of the lower ileum, since the writer did not find this definite relation to exist either with regard to the severity, acuteness, or purity of the case. Some cases there no doubt are in which the mucus flakes of the rice-water stools directly taken from the contents of the lower ileum are crowded with the comma bacilli, but in a considerable percentage of typical cases this condition does not obtain; there are comma bacilli present, but on the whole they appear scarce. The epithelial flakes detached and suspended in the contents of the ileum, as well as the epithelial flakes loosened but not quite detached from the mucous membrane, both of the villi and of the mouth of the Lieberkühn's follicles, contain comma bacilli as well as other bacteria. In sections through the hardened mucous membrane of the ileum one can find sometimes comma bacilli as well as other bacteria within the tissue of the superficial mucosa denuded of epithelium, and in the cavity of the Lieberkühn's follicles, and in spaces artificially produced by the loosening and detachment of the epithelium of the Lieberkühn's follicles, but their presence in these localities is due to immigration from the free surface into a disorganised mucous membrane, and neither bears any relation to the onset nor to the severity of the illness. Where the comma bacilli are scarce in the intestinal contents, they, or other bacteria, are altogether missed from the mucosa; where they are abundant in the contents and on the surface, and where the moribund stage lasted for hours, they penetrate from the surface into the disorganised mucous membrane.

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[1] Conferenz zur Erörterung der Cholerafrage, *Berliner kl. Woch.*, 31, 1884.

In the illustrations accompanying this part, comma bacilli are shown as occurring in fresh mucus flakes of typical acute cases of Asiatic cholera, and it will be seen from these that, as regards size, curvature, and numbers, there exist considerable differences. The comma bacilli are met with in almost all cases of Asiatic cholera, beginning with those that show as yet only diarrhœa, more or less profuse, up to those that have shown all the typical characters, with vomiting and purging of copious rice-water evacuations. After the acute stage has passed, and the typhoid stage has set in, the comma bacilli become less numerous, and gradually disappear, so that when after three, four, or five days the evacuations again assume the character of fæces, the comma bacilli are either only found with difficulty or are altogether missed; in fact, in cases in which they are scarce at the earlier stages, they are not to be seen later than the third day.

If cholera stools, particularly rice-water stools, are kept for a day or so, one meets with comma bacilli which have formed spirilla; some are wavy threads, others are distinctly corkscrew-shaped, some short, others long; in dried and stained preparations many of these spirilla are seen to be chains of comma bacilli; spirilla are occasionally found even in the fresh stools or fresh mucus flakes, but as a rule the comma bacilli are present as single vibrios or as dumb-bell vibrios, i.e. S-shaped forms. As regards the amount of curvature and length of the individuals there exist great variations (*see* figs. 87 and 88).

The comma bacilli of Asiatic cholera show on cultivation in nutrient gelatine well-defined appearances, which together with their morphological characters enable us to recognise them, so much so that in suspicious cases of cholera their demonstration by cultivation in the evacuations is of diagnostic value. But in connection with this it must be borne in mind that in some early cases or in non-typical cases their demonstration by the culture test, owing to the vast predominance of other bacteria, is a matter of some difficulty. Where they are present in large numbers their demonstration by the culture test is a matter of comparative ease. All that is necessary is to place a small particle of the evacuation in a few (8–10) cubic centimetres of sterile (well boiled) salt solution, shake it up well, and then with a droplet of this inoculate nutrient gelatine, contained in a test-tube, liquefy the gelatine in warm water, shake up and then pour it on sterile glass dishes for the object of plate cultivations. A particle of a mucus flake of a rice-water stool, rich in the comma bacilli, diluted with several cubic centimetres of sterile salt solution, and a trace of this mixture used for plate cultivation, yields large numbers of colonies of the comma bacilli. These show themselves (at 20° C.) after thirty-six to forty-eight hours as greyish white minute specks barely visible to the unaided eye; after three days they are distinctly visible as small, clear, circular depressions, due to liquefaction of the gelatine within this depression. In the centre of the depression is a round, greyish speck surrounded by clear, liquefied gelatine; looked at under a lens this speck appears granular, with a more or less uneven margin; in the centre of the speck is a more opaque, round granule. Each of these colonies gradually enlarges; the zone of clear, liquefied gelatine becomes broader, and the whitish central speck or patch enlarges; where the colonies lie close together at the outset, the progressing liquefaction soon produces a coalescence of the adjoining colonies, and then we get a number of circular zones of clear, liquefied gelatine, each with a central grey patch, the zones being fused together at the points of contact. When during further growth the gelatine becomes liquefied over extensive areas, the outlines of the original colonies are lost, and on the surface of the clear, liquefied gelatine are thin, filmy flakes, and at the bottom minute whitish granules. In all stages, before and after the liquefaction of the gelatine has become well pronounced, there are found under the microscope rapidly motile vibrios, single commas, S-shaped dumb-bells, and numerous longer or shorter spirilla, chains of commas, some wavy, others uniformly spiral. The above-named 'granules' and 'flakes' are masses of commas and spirals intimately matted together, and when examined in the fresh state look like so many clumps of different shapes, rapidly revolving.

In stab culture in gelatine the characters of these comma bacilli are also well marked; they are accurately represented in Plate XXX., and need not further be described.

After several days to a fortnight, there is noticed a distinct pellicle on the surface of the liquefied gelatine: this latter is clear, but contains a few whitish granules marking the outline of the funnel-shaped channel of liquefied gelatine.

Alkaline broth (at 36–38° C.) is slightly turbid even after twenty-four hours' growth: the turbidity increases during the succeeding days. After a week or so the superficial layers become gradually clearer, and this clearing extends steadily and insensibly towards the deeper layers; hand in hand with this goes the deposit of a greyish white powdery precipitate; a more or less distinct pellicle is noticed after a few days, and gradually increases in thickness. Under the microscope the comma bacilli in the fluid and in the pellicle are seen to be connected with beautiful spirilla, some of these of great lengths, some as many as twenty to thirty turns, the long spirilla more or less plicated and bent.

The growth on agar mixture is not characteristic, being in the form of thin, translucent patches and films, with rounded or knobbed outline, assuming as growth goes on, i.e. after some days, a slight brownish tint.

On boiled potato the comma bacilli grow only at temperatures above 25° C.; at 36° they form after a few days a thick, smeary, brown film. Comma bacilli grow well and rapidly, if mucus flakes of a cholera intestine containing numerous comma bacilli are placed on linen kept damp. After twenty-four hours the comma bacilli have increased to an enormous extent, almost to the exclusion of other bacteria originally present, provided these were at the outset less numerous than the comma bacilli. Löffler has photographed the flagella, after staining by means of a new method; there are always present several flagella at one end of each comma bacillus.

Comma bacilli grow well and luxuriantly between 17° and 40° C., on almost anything—paste, boiled egg, turnip, cucumber, cabbage, bread, meat, various fruits. &c. They grow best at 35–37° C., if the medium is faintly alkaline; but they grow also on neutral medium, and even on some media which are slightly acid, like potato and fruit. The writer has seen comma bacilli which, having started on nutrient gelatine, kept for a few days at 20° C., continued to grow slowly but steadily, the gelatine being then kept at 15–16° C. Comma bacilli gradually die off if nutriment is insufficient, e.g. in distilled water; they are gradually killed in fæcal matter; and they do not grow well in the absence of oxygen.

In all cultivations of the comma bacilli one meets with forms which differ from the typical curved, cylindrical vibrios, in so far as they are much thicker, plano-convex, bi-convex, or even approaching the spherical shape with a clear vacuole in the middle. In well-stained and well-washed specimens also the most typical comma bacilli show, within the sheath, the protoplasm collected at the ends—as a granule at each end—whereas the middle part remains clear. The above atypical forms are merely further developments of their normal form, caused by the enlargement of the central clear space or vacuole. Such atypical forms are to be met with in all cultures; their number, however, varies greatly with the character of the culture. If comma bacilli, originally derived from the cholera intestine, are carried through many successive sub-cultures in gelatine, say one or two dozen, the number of such atypical bi-convex or spherical forms is found greatly increased after a few days' growth. The writer has in his possession cultures of choleraic comma bacilli obtained from Calcutta direct from the choleraic intestine. For six months, sub-cultures were carried on through fifteen or twenty generations; all cultures made in broth, in gelatine, or in agar mixture by this time showed during the first few days all and every comma bacillus of a spherical shape; these were possessed of active motility and were of different sizes. After several more days, typical curved vibrios gradually made their appearance in the culture until only these were present. Plate cultivations prove most decidedly that at all times the culture is pure, but in every sub-culture the above spherical actively moving forms are at first present in large numbers (fig. 91).

The writer has in another place shown that such actively motile spherical forms by division give origin to two or even three comma-shaped, or more or less semicircular comma bacilli. The spherical forms are met with in numbers also in agar culture, if the agar mixture is at starting of neutral reaction, but they are abundant in all media (broth, gelatine, agar) after the cholera culture has been carried through many generations of sub-cultures. Such modified comma bacilli grow in gelatine somewhat more slowly than the recent ones, i.e. those recently derived from the cholera intestine.

Comma bacilli under culture rapidly undergo degeneration into granular *débris*; in fact, a good deal of the white deposit in gelatine and broth cultures is due to their *débris*. Degeneration goes on comparatively more rapidly in agar culture than in gelatine cultures. It is a notorious fact that on the surface of agar cultures the whole of the growth is found dead after from a few to several months, so that no new culture can be started from such an old culture. This degeneration and death occur sooner or later in all cultures; this alone proves sufficiently that the comma bacilli do not form permanent seeds or spores. Koch has proved by many experiments of drying that the comma bacilli are invariably killed by drying, unlike spore-bearing bacilli, and that at no time do the comma bacilli form spores. Heating cultures (old or recent) of comma bacilli to 60° C. for five minutes invariably kills the cultures—a proof that no spores are formed. The assertion of Hueppe that the terminal granules observed in comma bacilli are spores, viz. arthrospores, is definitely negatived by the above direct experiments.

Comma bacilli of cholera mucus flakes or of cultures, recent or old, are killed by acids, e.g. a fluid containing 0·2 per cent. hydrochloric acid,[1] so that the normal acid fluid of the stomach kills the comma bacilli; also this is opposed to there being spores present in the comma bacilli.

The comma bacilli occur in cholera as a rule only in the cavity of the small and large intestines, chiefly the lower part of the ileum and large intestine; no bacteria occur in the blood or other tissues. Comma bacilli and also other bacteria may and sometimes do immigrate into the disorganised tissue of the wall of the ileum, and in a few cases have been traced even as far as the liver and gall bladder; but in the large majority of cases the comma bacilli are limited to dead tissues, i.e. the contents of the ileum and large intestine and the superficial dead and disorganised parts of the internal surface of the mucous membrane of the ileum. For this reason Koch maintained that the disease is caused by a chemical poison—a kind of ptomaïne — which, being elaborated by the comma bacilli within the ileum, is absorbed into the blood, and hereby sets up the disease cholera. We have mentioned above that the facts of the case prove that the comma bacilli are not found in the mucous membrane of the ileum unless as the result of secondary immigration, and therefore the explanation of the chemical poison elaborated by the comma bacilli in the cavity of the intestine being absorbed is not well supported; for it would require us to assume that at the time that the comma bacilli are notoriously few, i.e. at the onset of the disease, sufficient of the chemical poison is already present to produce the symptoms of cholera, whereas, as a matter of fact, the comma bacilli are only present in large numbers—and this only in a minority of cases—when the typical disease with typical rice-water stools has well set in. But it must be evident from the nature of the disease, that at this stage the intestinal wall can hardly be in a state capable of absorbing anything; on the contrary, large quantities of fluid are poured out from its mucous membrane. If the comma bacilli were present in considerable numbers in the mucous membrane at the onset of the disease, one could understand that producing the chemical poison in sufficient quantities the absorption of this would set up the symptoms of the disease; but the actual facts follow in exactly the reverse order, viz. the comma bacilli are scarce at first, and *cæteris paribus* become more numerous as the symptoms of the disease become more pronounced, and when they are found abundant the typical disease has well set in. The comma bacilli in the cholera intestine are then present only in practically dead tissues, the fluid and detached mucus flakes of the contents of the ileum. And further, though the whole small intestine offers in typical acute cases the same appearances, the whole of the jejunum and ileum being filled with fluid and containing mucus flakes, yet we find the comma bacilli chiefly, generally solely, in the lower ileum, thus indicating that, like putrefactive bacteria, they increase in numbers as the large intestine is approached. The comma bacilli of Asiatic cholera produce in artificial cultivations toxic chemical products, cadaverine (Hueppe), such as are produced by various putrefactive bacteria; these products injected in sufficient quantities into rodents are capable of rapidly setting up intoxications leading to death. The comma bacilli of Finkler, and the comma bacilli of Deneke, although differing in cultural characters from the choleraic comma bacilli, produce the same toxic substance, cadaverine. Finkler's comma bacilli are not peculiar to the intestinal contents in sporadic cholera, as was first believed by Finkler and Prior, for Frank and Kartulis have not found them in cases of sporadic cholera, but they have been isolated by Brieger from the fæcal matter of the normal intestine; yet, as we have pointed out, these comma bacilli of Finkler are capable of producing the very same toxic substance, cadaverine; so also the comma bacilli of Deneke, found by him in stale cheese. There are other notorious saprophytes which have been proved to be capable of producing similar toxic principles.

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[1] Koch, Watson Cheyne (*Brit. Med. Journal*, 1885).

The comma bacilli, then, do not differ from some putrefactive bacteria in this power of producing toxic substances in certain albuminous culture fluids. Van Ermengem[1] has first shown that those chemical poisons are not produced by the choleraic comma bacilli in all culture media to the same extent; while in broth and gelatine little of them is produced, in aqueous humour and in serum they produce them rapidly in large quantities. Further, Hueppe has shown that in white of egg (growing anaërobically in the egg) the choleraic comma bacilli rapidly produce toxic cadaverine. The choleraic comma bacilli produce in artificial cultures indol and nitrites (Salkowski), like many putrefactive bacteria.

Bujwid[2] was the first to show that broth cultures of comma bacilli, incubated at 37° C., give with ordinary hydrochloric acid, or nitric or suphuric acid, a definite colour reaction of red-purple—the cholera red. Dunham[3] has found that for this reaction the presence of peptone in the broth is essential, and that other comma bacilli (Finkler's and Deneke's) also show this reaction, though in a lesser degree. Salkowski showed that this reaction is closely associated with the formation of indol and nitrites in the culture fluid by the comma bacilli. Thus far we see, then, that in chemical respects the choleraic comma bacilli do not differ from other putrefactive bacteria.

Since they are capable of producing toxins, it follows that when they have an opportunity of multiplying sufficiently they produce a sufficient amount of the toxic substance cadaverine, and thereby are capable of producing acute poisoning. The experiments of Van Ermengem prove that where this chemical substance is produced in sufficient quantities (e.g. in aqueous humour or serum) even small quantities injected into rodents (guineapigs) produce acute intoxication. Van Ermengem further showed, and in this his views have been confirmed and extended by the observations of McLeod and Mills ('Reports from the Laboratory of the Royal College of Physicians,' Edinburgh, vol. i.), that if in the intestine of a guineapig the comma bacilli can be brought into rapid multiplication (*see* below), the intestinal fluid teeming with the comma bacilli contains those same toxic principles in a concentrated form, so that a small quantity of it injected into a fresh guineapig produces intoxication and death. In order to produce a similar intoxication in guineapigs with broth cultures or gelatine cultures it is necessary to inject considerable quantities of these cultures. In some cases it is, however, possible to produce a septicæmic infection in mice or guineapigs by subcutaneous injection of cultures of comma bacilli. Koch has succeeded in mice, Ferran and Dr. D. D. Cunningham have succeeded in guineapigs, the writer has in several instances by using large doses of culture fluid (0·5–2 c.c.) succeeded in producing such septicæmic infection in guineapigs, equally with choleraic comma bacilli or with Finkler's comma bacilli, the blood and the tissues containing crowds of the comma bacilli. Dr. D. D. Cunningham has in several instances succeeded in producing such septicæmic infection and death, the blood, the exudation on the serous covering of the intestine, and the intestinal contents containing an abundance of comma bacilli.

All these experiments, however interesting they may be, do not throw any real light on the question whether or not the comma bacilli are the real cause of cholera; they only show that towards rodents the choleraic comma bacilli behave like so many other notoriously putrefactive microbes, e.g. the Naples bacillus of Von Emmerich, the bacterium of Brieger isolated from normal human fæcal matter, the bacillus of Bienstock, the comma bacillus of Finkler, &c.

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[1] *Recherches sur le microbe du Choléra Asiatique*, Brussels, 1885.

[2] *Zeitschrift f. Hygiene*, II., p. 52.

[3] *Ibid.*, p. 337.

But it is asserted that the comma bacilli when introduced into the small intestine in a living state are capable of setting up an acute illness resembling Asiatic cholera, and death.

Koch in his first pamphlet on cholera (*l.c.*, p. 27) told us that he had made every imaginable effort to produce cholera in animals experimentally. The experiments of feeding white mice with cholera dejecta, first made by Tiersch and then by Burdon Sanderson, were repeated by Koch over and over again on fifty white mice fed with this material (dejecta of cholera patients, and the contents of the intestine of cholera corpses) and with choleraic material after it had begun to decompose, but no result whatever followed; the mice remained healthy. 'We then made experiments on monkeys, cats, poultry, dogs and various other animals that we were able to get hold of, but we were never able to arrive at anything in animals similar to the cholera process. In precisely the same manner we made experiments with the cultivations of comma bacilli; these were given as food in all stages of development. When experiments were made by feeding animals with large quantities of comma bacilli, on killing them and examining the contents of their stomachs and intestines with a view to find comma bacilli, it was seen that the comma bacilli had already perished in the stomach, and had usually not reached the intestinal canal. . . . The comma bacilli had been destroyed in the stomachs of these animals. . . . The experiment was therefore modified by introducing the substances direct into the intestines of the animals. The abdomen was opened, and the liquid was injected immediately into the small intestine with a Pravaz syringe. The animals bore this very well, but it did not make them ill. We also tried to bring the cholera dejecta as high as possible into the intestines of monkeys by means of a long catheter. This succeeded very well, but the animals did not suffer from it.' 'I must also mention,' says Koch, 'that purgatives were previously administered to the animals in order to put the intestine into a state of irritation, and then the infecting substance was given, without producing any different result. The only experiment in which the comma bacilli exhibited a pathogenic effect, which therefore gave me hope at first that we should arrive at some result, was that in which pure cultivations were injected directly into the blood-vessels of rabbits or into the abdominal cavity of mice. Rabbits seemed very ill after the injection, but recovered after a few days. Mice, on the contrary, died from twenty-four to forty-eight hours after the injection, and comma bacilli were found in their blood. Of course they must be administered to the animals in large quantities; and it is not the same as in other experiments connected with infection, where the smallest quantities of infectious matter are used, and yet an effect is produced. In order to arrive at certainty as to whether animals can be affected with cholera, I made inquiries everywhere in India as to whether similar diseases had ever been remarked amongst animals. In Bengal I was assured such a phenomenon had never occurred. This province is extremely thickly populated, and there are many kinds of animals there which live together with human beings. One would suppose, then, that in that country, where cholera exists in all parts continually, animals must often receive into their digestive canal the infectious matter of cholera, and in just as effective a form as human beings, but no case of an animal having an attack of cholera has ever been observed there. Hence I think that all the animals on which we can make experiments, and all those, too, which come into contact with human beings, are not liable to cholera, and that a real cholera process cannot be artificially produced in them.'

Starting from the idea that the comma bacilli are killed by the gastric juice, and that in order to develop their pathogenic powers they have to get unscathed and living into the small intestine—their natural breeding-ground—it occurred to Koch[1] that this difficulty might be obviated by first neutralising or making alkaline the contents of the stomach, and introducing *per os* the comma bacilli. He therefore kept guineapigs for twenty-four hours without food, and then injected into their stomach *per os* 5 cubic centimetres of a 5-per-cent. watery solution of carbonate of sodium. This does not noticeably injure the stomach, and, as direct observation proved, kept the contents of the stomach in an alkaline condition for three hours. Some minutes (twenty) afterwards he introduced by catheter 10 cubic centimetres of a cultivation of the comma bacilli in meat infusion.

The result is noteworthy. Seven guineapigs thus experimented upon remained perfectly well: 'They were killed after twenty hours,' says Koch, 'and the contents of their stomach, intestine, and cæcum were examined by gelatine plate cultivations. In six of the seven animals the cholera bacteria could be demonstrated in the small intestine. The experiment had thus in so far succeeded that the cholera bacilli had passed uninjured through the stomach, but they had not set up any disease in the animals.' Similar experiments were them made on eight other guineapigs. These animals also remained quite healthy. Finally four guineapigs were similarly experimented upon (5 c.c. of solution of sodium carbonate, then 10 c.c. of cultivation of the comma bacilli in meat infusion); three remained well, the fourth appeared ill next day, looked shaggy and did not eat; on the following day it was very ill; paralytic weakness of the posterior extremities came on, the respiration was weak and slow, the head and extremities were cold, and the animal died in this condition. On *post-mortem* examination the small intestine was markedly reddened and full of a flakey, watery, colourless fluid. The stomach and cæcum contained a large quantity of fluid. 'The examination with the microscope and with gelatine plates,' says Koch, 'showed that the contents of the small intestine contained a pure cultivation of the choleraic comma bacilli.' 'That this one animal only should have died, out of a series of nineteen, uniformly experimented upon, suggested some peculiar condition that had obtained in this one animal, and as a matter of fact on examination it was ascertained that this animal had aborted immediately before the injection, and on *post-mortem* examination it was found that the abdominal walls were very flaccid and the uterus still greatly enlarged. This led me to the idea that either the abortion *per se*, or perhaps its unknown cause, had acted on the other abdominal organs, more especially on the small intestine, in such a way as to produce a temporary relaxation with arrest of peristaltic movement; and thus had rendered it possible for the comma bacilli to remain longer and gain a footing in the intestine.' This conclusion appeared to Koch justifiable, inasmuch as by direct experiment he thought he had proved that the contents of the stomach pass too rapidly into, and through the small intestine, and that the comma bacilli could only unfold their poisonous action, i.e. could produce the chemical poison, if they had time to remain there and to multiply. Consequently if they were not delayed in their passage through the small intestine they would not multiply there, and once in the cæcum, where the reaction is acid, they would become harmless. To this method of reasoning, one may be allowed to take exception, Koch shows by direct experiment that even twenty hours after injection the comma bacilli can be recovered from the small intestine in a living state. Now the most important character of all pathogenic bacteria is this, that when introduced into the particular tissues suitable for their propagation they set up their pathogenic power. How is it, then, one might reasonably ask, that the comma bacilli, if even only for a few hours in the small intestine, do not in swarms invade the epithelium and superficial layers of the mucous membrane? Koch does not, and of course cannot, deny that all absorption of the chyle must take place in the small intestine, and since the comma bacilli are much smaller than the large chyle globules, and are possessed of spontaneous mobility, it follows of necessity that the comma bacilli can and must readily pass into the epithelium and the superficial layers of the mucous membrane; and since the epithelium and the superficial mucous membrane, according to Koch's own statement and belief, are the suitable nidus for the multiplication and action of the comma bacilli, all conditions would therefore here exist which are required for their settling down and acting. Add to this that the 10 c.c. of a broth culture injected, containing millions and millions of comma bacilli, are subject to absorption by the small intestine for twenty hours (*see* the above-mentioned observations of Koch), and that such vast crowds of comma bacilli in a few hours kept at the body temperature ought to yield a most formidable host of descendants, and grave doubts must arise as to the tenability of Koch's explanation.

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[1] Conferenz zur Erörterung d. Cholerafrage, Berlin, May 1885.

But to continue. In order to produce a condition similar to the one in the above single successful experiment on the guineapig, Koch injected tincture of opium into the peritoneal cavity after the introduction of the sodium carbonate and the cultivation of the comma bacilli: this answered well for achieving positive results. Immediately after the administration of the 10 c.c. of the culture of the comma bacilli, 1 c.c. of German tincture of opium for every 200 grms. of the animal's bodyweight was injected into the peritoneal cavity: the animals became narcotised for half an hour, and died after one and a half to three days, with the same symptoms as the above guineapig. 'Eighty-five guineapigs have been infected in this way with cholera.'

Now the following criticisms can, we think, be justly applied to these experiments: (1) According to Koch's own showing, it cannot be the narcosis which is essential, even allowing for the present that relaxation of the intestine may have been produced by the intraperitoneal injection of opium tincture, since alcohol alone, injected by Koch into the peritoneal cavity, produces the same result; he says that thereby 'we were most successful in making the animals susceptible to the cholera infection.' (2) Can narcosis of the animal be produced by opium without furthering in the least the process of the experiment? This has been tried over and over again; watery extract instead of tincture of opium is injected into the peritoneal cavity, and narcosis lasting for one hour is produced, but the animals remain well; tincture of opium is subcutaneously injected, the animals fall into narcosis, lasting for from forty to eighty minutes, but no result is obtained from the previous introduction of the comma bacilli; in fact, the experiment as designed by Koch was repeated by the writer on a large number of guineapigs, thirty in all, but instead of producing narcosis by injection of tincture of opium into the peritoneum, he produced it by intraperitoneal injection of watery extract of opium, or subcutaneous injection of tincture of opium and watery extract of opium, but all in vain. The comma bacilli used were of recent broth culture, or of gelatine culture, and were beyond question or doubt the choleraic comma bacilli. (3) It is not proved that injection of tincture of opium into the peritoneal cavity produces relaxation of the intestine and arrest of the peristaltic movement; there is no proof given for this by Koch as regards the guineapig; on the contrary, there are experiments on record made on the dog, when the result of such injection was quickening of the peristaltic movement.

From all these considerations it appears unwarranted to conclude, as Koch does, that the multiplication of the comma bacilli in the small intestine, and their fatal action by the chemical products they elaborate, take place on account of a relaxation and arrest of the peristaltic movement by the opium. Another explanation appears much more probably correct. It is this: provided the intestine is first made diseased, either in consequence of slight peritonitis, as was probably the case in the guineapig that had aborted, or in the experiments in which tincture of opium or alcohol alone was injected into the peritoneal cavity, or from other reasons, the comma bacilli that are present in the intestinal cavity undergo rapid multiplication, and by their chemical products, not only increase the disorder of the mucous membrane, but eventually poison the animal. And from this we conclude, further, that a multiplication of the comma bacilli can and does take place only when the intestine is previously brought into a diseased state. Under this view all Koch's and Van Ermengem's results become at once intelligible.

We maintain, then, that the living choleraic comma bacilli, in however large a number they be introduced into the small intestine, are quite innocuous; but they are rendered capable of great multiplication if the intestine is previously, from some cause or another, diseased. The chemical products of such multiplication act as poisons analogous to the ptomaïnes obtained from other putrefactive bacteria.

That this is the true explanation we find proof in some of Koch's experiments with other bacteria, notably with Finkler's and Deneke's comma bacilli. With both these organisms, on experimenting in the above manner, he obtained positive results; not so constantly, it is true, but still he did obtain positive results, not identical, but similar. Of course it is not to be expected that, seeing these are three different species, they would act in the same manner. Finkler[1] published a large series of experiments, in which, with his comma bacilli, and after the method of experimentation employed by Koch, he produced results identical with those gained by Koch with the choleraic comma bacillus. There can be no doubt, from what has been shown above, that Finkler's comma bacillus has nothing to do with cholera nostras, or with any other infectious disease, but that it is simply a putrefactive organism. And on the same grounds Koch's comma bacillus cannot be said by these experiments to have been proved to have a causal relation to Asiatic cholera, any more than has Finkler's comma bacillus, or any of the other species of septic bacteria that are capable of producing chemical poisons analogous to ptomaïnes. All that can be said is that, provided that conditions are established by which the choleraic comma bacilli are enabled to grow and multiply in the intestinal canal, these chemical poisons may be produced. A very instructive and parallel case is found in the so-called typhoid bacillus. As is now generally held, the experiments published by Fraenkel and Simmonds, in which they maintain that they have produced typhoid fever and death in rabbits after injection of large quantities of cultivations of the typhoid bacilli, do not prove any real infective action of the typhoid bacillus for the rabbit; it has been conclusively proved that this result is entirely due to certain chemical substances generated by the typhoid bacillus in the cultivations

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[1] Ergänzungsheft z. *Centralbl. f. allg. Gesundh.*, I., 5 and 6.

(Sirotinin, Beumer and Peiper). This pathological condition can be produced, entirely apart from the bacilli by chemical substances (typhotoxin) produced by them in cultivations, and as is the case in other similar toxic substances the severity of the abnormal state depends on the quantity injected. Moreover, it has been shown by Beumer and Peiper that by the injection of a small quantity of the chemical substance, a refractory state against an otherwise fatal dose of the same substance can be produced (Beumer and Peiper, 'Zeitschr. f. Hygiene,' II., p. 110).

Dr. D. D. Cunningham ('Scientific Memoirs, by Medical Officers of the Army of India,' Part VI., Calcutta, 1891) has shown that there are typical cases of acute cholera in which no comma bacilli occur, and further he has made the important discovery that the comma bacilli occurring in Asiatic cholera belong to a number of well-defined species, differing from one another in size, in the rapidity with which they liquefy the gelatine, and in the manner in which they grow on potato, so that these facts alone enable Cunningham to deny the causal relation to cholera claimed for Koch's comma bacilli.[1]

From these experiments, and similar ones, we conclude that the disease thus produced in guineapigs has no claim to be considered as Asiatic cholera, since Finkler's comma bacillus and Deneke's bacillus induce, under the same method of experimentation, a similar fatal disease. Besides, the disease thus induced in guineapigs differs in this important respect from cholera, that the temperature of the animals is at first raised, and only shows a fall when the animal is really moribund.

Various species of comma bacilli are known : Finkler's, Deneke's (cheese spirillum), the spirillum of noma, spirilla in various mucous substances isolated and described by Weibel,[2] and others.

Gamaleia[3] has shown that a vibrio in many respects similar to, if not identical with, Koch's comma bacillus of Asiatic cholera causes a septicæmia in fowls and pigeons similar to, but not identical with, fowl cholera ; it is the one he named vibrio Metschnikoff. He further stated that the two vibrios are in so far inimical to each other as that an animal that has survived the disease produced by one is possessed of immunity against the other. Pfeiffer, however, shows ('Zeitschr. f. Hygiene,' VII., 3), that these last assertions of Gamaleia are incorrect. While he confirmed Gamaleia as to the septicæmic effect of the vibrio Metschnikoff on pigeons (with copious occurrence of the vibrios in their blood), he proved that morphologically, culturally, and experimentally (as tested on pigeons and guineapigs), they are two different species, and that there exists no inimical action of one against the other.

Pfeiffer has also shown that Gamaleia's assertion as to the susceptibility of pigeons to infection with the choleraic commas (it is in pigeons that Gamaleia maintained that he had succeeded with his protective inoculations) is incorrect, pigeons being insusceptible to such infection. The writer can fully confirm Pfeiffer in this, since, even with large doses of cultures of the choleraic comma bacilli injected into pigeons, he has not been able to produce any result whatever; moreover, on injecting into the pectoral muscle of pigeons as much as 2–3 c.c. of broth culture, and searching by culture test and cover-glass specimens for comma bacilli twenty-four hours later, no trace of them can be discovered; the pigeons remain perfectly well.

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[1] It ought to be stated that recently Dr. Friedrich directly traversed these statements of Cunningham (*Arbeiten aus d. k. Gesundheitsamte*, Berlin, 1892). The writer, however, has been able fully to confirm Cunningham's statements as to the permanently different cultural characters of his various species of choleraic comma bacilli.

[2] *Centralbl. f. Bact. und Parasit.*, II., No. 16; IV., Nos. 8, 9, 10.

[3] *Annales de l'Institut Pasteur*, No. 9, 1888, p. 482.

DYSENTERY

This is an affection of the large intestine, occurring in the human subject, chiefly in hot climates. It consists in a hæmorrhagic effusion into, and necrosis of, the mucous membrane; in the affected parts the mucous membrane (the mucosa) is the seat of extensive engorgement of the blood-vessels, stasis of, and hæmorrhage from, the veins and capillary blood-vessels; at the same time there is exudation of cellular and fluid matter, inclusive of blood *en masse*, into the cavity of the intestine, and of course in the evacuations; the hæmorrhage is followed by necrosis of the mucosa in the area of the hæmorrhage, with a reactive inflammation surrounding the necrotic parts, both in the mucosa and sub-mucosa; in consequence of this inflammation, the necrotic parts become gradually loosened and detached, and the deficiency is partly filled with the products of the inflammation. In the affected parts, the size of which varies from that of punctiform petechiæ, to that of areas several inches in length, the tissue elements undergo the change known as coagulation necrosis; though they retain their outline for a little time, their substance appears opaque, granular, and they do not take the ordinary stains; the epithelium of the surface is loosened, or altogether lost, from extensive parts of the surface; the lymphatic tissue of the mucosa, and the epithelium lining the Lieberkühn's crypts, which becomes loosened and detached from the membrana propria, fail to take the ordinary stains, become granular, opaque and dry looking, and are gradually transformed into a granular detritus. Around the part thus affected numerous leucocytes accumulate in the mucosa and sub-mucosa, and these leucocytes gradually invade the necrotic portion.

The serous covering of the intestine, as well as the mucous membrane of almost the whole of the large intestine, is much congested. The mesenteric lymph glands are swollen and highly congested. As a frequent sequela there occurs formation of abscess in the liver.

Lösch (Virchow's 'Archiv f. pathol. Anatomie,' 1875, Band LXV., p. 196) was the first to discover the amœba coli in great numbers in a case of ulcerated large intestine in the human subject. This case, in all its clinical and pathological symptoms, resembled true dysentery.

Kartulis ('Centralbl. für Bact. und Parasit.,' VII., 2) has shown that in the cases of tropical dysentery which he examined, numerous *amœbæ* (amœba coli of Lösch) were present in the characteristic sanguineous stools showing active amœboid movement, and he gives good reasons for considering these the cause of the dysentery; though others who had met with similar amœbæ in intestinal diseases in Russia (Massiatin, 'Centralbl. für Bact. und Parasit.,' VI., Nos. 16 and 17) did not think so.

Further, Kartulis has shown that in twenty cases of abscess of the liver complicating dysentery he found in every one of them the same dysentery amœbæ; they could be seen in sections through the wall of the abscess, but in the pus of the abscess cavity he did not find them.

A considerable amount of literature exists at present on the occurrence of amœbæ in certain forms of dysentery, chiefly those that run a chronic course, and on their absence and the presence of various species of bacilli in other forms of acute dysenteric inflammation of the large intestine. While some have confirmed Kartulis (Osler, Councilman, Maggiora, and others), others have missed the amœba, but describe various species of bacteria as connected with the disease. From the careful bibliography collected by Maggiora ('Centralblatt für Bact. und Parasit.,' XI., Nos. 6 and 7) there can be no doubt that what is clinically spoken of as dysentery, is not in etiological respects one single disease, since some dysenteric affections are, others are not, caused by the amœba coli.

CHAPTER XXII

INFANTILE DIARRHŒA OR SUMMER DIARRHŒA

THIS disease, causing considerable mortality in children, occurs in an epidemic form in the summer months in many English towns; in some, as Leicester and Nottingham, to a larger extent than in others. Dr. Ballard, who has for several years been investigating this disease, formulates in his report ('Supplement to the Report of the Medical Officer of the Local Government Board,' 1887, p. 7) as the causes of the diarrhœa the following conclusions:—

> 'That the essential cause of diarrhœa resides ordinarily in the superficial layers of the earth, where it is intimately associated with the life processes of some micro-organism not yet detected or isolated.
>
> 'That the vital manifestations of such organism are dependent among other things, perhaps principally, upon conditions of season and on the presence of dead organic matter, which is its pabulum.
>
> 'That, on occasion, such micro-organism is capable of getting abroad from its primary habitat, the earth, and having become air-borne, obtains opportunity for fastening on non-living organic material, and of using such organic material, both as nidus and as pabulum, in undergoing various phases of its life history.
>
> 'That in food, inside as well as outside the human body, such micro-organism finds, especially at certain seasons, nidus and pabulum convenient for its development, multiplication, or evolution.
>
> 'That from food, as also from the contained organic matter of particular soils, such micro-organism can manufacture by the chemical changes wrought therein through certain of its life processes a substance which is a *virulent chemical poison*; and
>
> 'That this chemical substance is, in the human body, the material cause of epidemic diarrhœa.'

It will be observed that this provisional hypothesis is sufficiently elastic to include, as a common cause of diarrhœa, chemical products of bacterial life manufactured indifferently within or outside the human body. Elasticity, to this extent, of a provisional hypothesis has been necessary for the reason that, in the present state of our knowledge, certain cases and groups of cases of diarrhœa, not distinguishable from epidemic summer diarrhœa, have now and again been found to possess the faculty of being directly communicable from person to person. The account of Dr. Bruce Low's experience at Helmsley, in Yorkshire, appended to the above report (Appendix H) is illustrative of this class of cases.

It will be obvious that in the stools of such infective cases of diarrhœa the hypothetical organism causative of the malady may be looked for with good hope of success.

A point worthy of further inquiry, and hitherto rendered suspicious by many health officers, is this, that infants fed from 'the bottle' are the principal victims of fatal diarrhœa in summer.

Pathology (Dr. Ballard's Report, pp. 13 and 14):—

> 'In the bodies examined there were marked pathological changes, not only in the intestines, but in all the viscera, and not alone in the viscera of protracted cases, but in those of infants the total duration of whose illness had not exceeded twelve or fourteen hours.

For the most part the intestines were empty, or only contained a little yellow fæcal matter, or a little opalescent mucoid fluid, or the surface was coated with some thick, creamy, catarrhal exudation. The amount of obvious hyperæmia of the mucous membrane of the stomach and intestines varied; sometimes there was observed some follicular ulceration both in the small and large intestines. Generally there was more or less inflammatory thickening of the mucosa, and even in the cases of only a few hours' duration denudation of the epithelium, both of the stomach and intestines. Now and then ecchymoses were seen, or even a little blood effused into the alimentary canal. The solitary and agminated glands of the small intestine were most prominent; the mesenteric glands were enlarged. The condition of spleen varied: it was sometimes congested, or exhibited hyaline degeneration of the arteries, or swelling of the Malpighian corpuscles with degeneration of the central portion of them. The condition of the liver varied. It was either congested, or pale and bloodless, the former condition prevailing in the cases of short, and the latter in those of longer duration; but in every case examined there was one invariable condition, viz. fatty degeneration of the liver cells, slight in cases of short (only a few hours') duration, but pronounced and extensive, or complete in all parts of the organ, when the illness had been protracted. The kidneys, even when normal to the naked eye, were invariably found to be diseased when examined microscopically, showing inflammatory and degenerative changes, intense glomerulo- and parenchymatous nephritis being demonstrated even in cases of very short duration. The lungs, although they might be in parts collapsed, presented marked evidence of acute catarrhal and interstitial pneumonia. The blood may be inspissated and coagulate imperfectly. There was nothing in the microscopical investigations of the tissues, blood, or excreta to indicate that in the cases which furnished the organs, blood, or excreta, the malady was due to any micro-organism developing within the alimentary canal or permeating any of the tissues.'

As regards microbes, various bacteria have been mentioned as occurring in the intestinal contents and in the stools in this disease, but there does not seem to be any relation proved to exist between them and the disease. From the writer's own observation he is prepared to say that among those microbes hitherto described as the cause of infantile summer diarrhœa, none can claim that distinction.[1] The following may be quoted here from Dr. Ballard's Report as an instance of an organism very similar to that of Gaffky that was found in an acute case of summer diarrhœa in the intestinal contents, penetrating also into the mesenteric glands, viz.:—

'The case was one of typical acute summer diarrhœa admitted into the hospital in Great Ormond Street, and which ended fatally with fits of eclampsia. In the cavity of the intestine there were found numerous mobile bacilli which in size and shape bore a certain resemblance to the bacilli known as occurring in typhoid fever. These bacilli were also found on microscopical examination of the sections of the swollen mesenteric glands, but were not numerously present there. From these glands cultivation experiments were made on nutritive gelatine; the bacilli were thus isolated and pure cultivations obtained. Comparing these cultures with those of the typhoid bacilli of Gaffky, a striking resemblance is noticed: (*a*) They look alike in microscopical specimens. (*b*) They grow alike in plate cultivation. (*c*) They grow alike in broth. (*d*) They are very much alike in stab and streak cultures on gelatine and on agar agar mixture.[2] Comparing the two in respect of their action on animals, it is found that when inoculated into white mice they produce in a large percentage of cases death under septicæmic appearances; the bacilli could be recovered from the heart's blood by cultivation. The differences between them, so far as can at present be seen, are: (1) That this bacillus from the case of infantile diarrhœa grows on gelatine more rapidly than Gaffky's typhoid bacillus; and (2) that the former has a somewhat greater resisting power to the action of perchloride of mercury than the latter.'

A severe form of diarrhœa occurring during the summer months amongst adults, not referable to consumption of poisoned food, and of a highly infectious nature, is recorded by Dr. Bruce Low. These forms of the disease evidently occupy an altogether different position from the infantile summer diarrhœa, as well as the choleraic attacks due to toxic effect of certain food stuffs. They are fully described in Dr. Ballard's Report, pp. 127–131.

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[1] Lesage describes in the green stools of infants affected with diarrhœa a species of minute rods slightly motile, which he considers the actual cause of the disease.

[2] There was a brief notice of this microbe in the *Annual Report of the Medical Officer of the Local Government Board* for 1886, p. 447.

CHOLERAIC DIARRHŒA DUE TO TOXIC EFFECT OF CERTAIN FOOD STUFFS

Various forms of acute disease are known which manifest themselves in severe gastro-enteric disturbance, vomiting, diarrhœa, pains in the abdomen and gastric regions, and more or less muscular prostration ; in some severe cases there is suppression of urine, cold skin, collapse, and even death. While these cases have a certain clinical resemblance one to another, they are etiologically different. In some the symptoms set in very soon, sometimes a few hours or an hour only after the introduction of the poisonous matter, while in others there is a distinct incubation period, varying from twelve, sixteen, to twenty-four hours, and even longer. In the latter cases the illness is always more protracted, and when death takes place the lungs, liver, and kidney are found congested, the spleen flaccid, and slightly enlarged ; in the stomach and intestines the mucous membrane is much congested, and there are even hæmorrhagic petechiæ, the mucosa is swollen, the epithelium of the surface partially loosened or altogether detached. In the cavity of the stomach and intestines there is a mucoid fluid occasionally containing extravasated blood ; but these appearances on the part of the alimentary canal are found also in the acute fatal cases of the first category.

In the first category of cases the disease is due to a chemical poison present in certain articles of food stuffs (ice cream, cheese, sausage, mackerel, tinned food materials) ; this poisonous substance has, in some instances, been isolated (Dr. Vaughan, tyrotoxicon), as a crystalline substance probably identical with certain crystalline bodies isolated by Brieger and others, and belonging to the group of toxins, e.g. cadaverine (pentamethylene diamine), in contradistinction to the ptomaïnes of Selmi, e.g. putrescine (tetramethylene diamine).

Now in some cases it has been shown that such toxin is formed in food stuffs by definite bacteria, having no action on proteid materials comparable to putrefaction in the ordinary sense, i.e. that process which starts with the change of proteid into peptone, decomposing this latter into leucin and tyrosin, forming at the same time ptomaïnes with the evolution of sulphuretted hydrogen and ammonia. The writer has had the opportunity of investigating several such forms of acute chemical poisonings brought about by the consumption of veal pie in one case (Dr. Ballard), pork pie in another, the latter outbreak reported by Dr. Spear in the Report of the Medical Officer of the Local Government Board ('Report of the Medical Officer,' p. 106, 1887–88). In both instances a bacterium was found in large continuous masses in the pies, and it was isolated and cultivated in artificial media. Mice fed with the pies succumbed rapidly under the appearances of severe gastro-enteritic symptoms ; mice fed with the artificial cultures succumbed in the same way ; but no microbes were found in the body, and the conclusion arrived at was that these bacteria are capable by their growth (in gelatine as well as in broth) of elaborating the toxic substance. The symptoms of disease in these mice set in after a few hours, as was the case in the human subject, and this clearly pointed to a chemical poison. The bacterium isolated from veal pie, as also that from the pork pie, produced when growing in gelatine a greenish blue colouring matter, which gradually increased in amount and became diffused through the gelatine. In the case of the veal pie bacterium, liquefaction of the gelatine began only after several weeks had passed, and it proceeded very slowly; it took several months to liquefy the gelatine (about 10 c.c.) in a test tube; the liquefied gelatine was thick and syrupy. In the case of the pork pie the bacterium did not liquefy the gelatine at all. Besides, the veal pie bacterium did not show any growth when kept above 25° C.; it grew best at 20–22° C., while the pork pie organism grew also at temperatures above this—at temperatures up to 36° C. So that we have here two distinct sets of acute chemical poisonings produced in food stuffs not showing any sign of what is ordinarily called putrefaction, poisons produced therein by two different species of bacteria, and which when they were introduced into the stomach set up gastro-enteritic disturbance.

A third similar instance was the Portsmouth beef-pie poisoning. Here a motile cylindrical bacillus was found, which did not liquefy the gelatine; mice fed with the beef pie or with the cultures of the bacillus succumbed with symptoms of acute gastro-enteritis. ('Report of Medical Officer of the Local Government Board for 1890–91').

The second category of gastro-enteritic disturbances produced by food stuffs, those with distinct incubation, are true infections.

Dr. Ballard's report of Welbeck and Nottingham ham-and-beef poisoning ('Report of the Medical Officer of the Local Government Board, 1880') gives an illustration of such infection. In this epidemic, ham was shown to have contained a peculiar short motile bacillus, which was found in large numbers in the vessels of the glomeruli and in the spleen of fatal human cases (fig. 152). Another similar epidemic occurred in Carlisle in 1889, and was due to certain pork pies. The pork and gravy stock from which the pies were made was proved to act poisonously by feeding mice on it. From such mice (congested lung) a bacillus was recovered by cultivation, which was proved to be the same as in the gravy stock. Cultures of this bacillus by feeding and subcutaneous inoculation produced in mice the same disease as the pork and the gravy stock—enteritis with sanguineous mucus, sanguineous diarrhœa, congestion of the lungs.

Gärtner ('Correspondenzblätter des allgem. ärztl. Vereins von Thüringen, 1888,' p. 573) found in the flesh of a cow dead with symptoms of acute diarrhœa, and also in the spleen of a man who partook of that meat and died in twelve hours, a peculiar species of bacillus—bacillus enteritidis Gärtner—which is motile, does not liquefy gelatine, and is very pathogenic for mice, guineapigs, and rabbits, both after feeding and after subcutaneous inoculation.

Gaffky and Paak described an epidemic of gastro-enteritis at Egelsdorf and Röhrsdorf amongst factory men who had eaten of meat and sausages made from horse flesh. The cause was found in a bacillus, 'sausage bacillus,' similar to, but not identical with, Gärtner's bacillus ('Arbeiten aus dem k. Gesundheitsamte,' Band VI., 2 and 3, 1890).

CHAPTER XXIII

INTERMITTENT OR MALARIAL FEVER—AGUE

THE pathological changes in intermittent fever, as observed in those malignant cases which terminate fatally, are chiefly those of the blood, the spleen, the liver, the marrow of bones, less constantly of the brain and kidneys. The blood in all cases shows a large number of black pigment granules singly and in clumps, free and enclosed in peculiar corpuscles (*see* below), which granules are proved to be derived from the colouring matter of the red corpuscles. These granules are either spherical, irregularly shaped, or oval, and they correspond to what is known as melanin. The spleen is always enlarged: this enlargement is due to an enlargement of the spleen pulp as well as of the Malpighian corpuscles; the latter are hypertrophied, in the central parts the lymph cells are swollen, many of these showing necrotic changes; in the spleen pulp the cells are greatly swollen, many contain several nuclei and masses of (black) blood pigment, the same pigment being present in the connective tissue of the trabeculæ, around, and in the wall of, the blood-vessels; also in the capillary vessels of the Malpighian corpuscles. This abundance of black pigment distinguishes the enlarged spleen in malaria from that occurring through other causes. In the red marrow of bones many of the marrow cells are much enlarged, and contain masses of black pigment; in the liver the blood-vessels of the lobules contain masses of black pigment granules, the liver cells themselves in many lobules showing fatty degeneration; in the interlobular connective tissue numerous round cells infiltrate the tissue, and in chronic cases these infiltrations lead to the new formation of connective tissue. In severe cases (febris perniciosa) necrotic changes of the liver cells around the central vein are noticeable (Garnieri), the blood in the latter being stagnated, and the capillaries leading to it full of leucocytes and pigment masses. In the kidneys severe changes occur, consisting of granular and fatty degeneration of the epithelium lining the convoluted tubes; around the arterial vessels of the cortex are found miliary aggregations of round cells. Pigment granules in larger and smaller masses are also found in the capillaries of the kidney, whereby many of them become plugged and impermeable. Also in the brain, pigment granules are found in capillary vessels, and in the severe form (febris perniciosa comatosa) plugging of them with pigment granules has been observed.

As to the etiology of the disease, most important discoveries have been made within the last few years. Laveran ('Comptes Rendus, 1882,' No. 17) and Richard (*ibid.*, No. 8) were the first who discovered in the blood of malaria cases, in the febrile stages, spherical or crescentic bodies consisting of a pale, homogeneous substance enclosing clumps of pigment granules; these bodies are possessed of cilia by which they are enabled to perform rapid movement. Laveran considered these bodies as the true cause of malaria, and identified them as protozoa. This discovery was a few years later (1885) confirmed and considerably amplified by Marchiafava and Celli. The credit of the important discovery of the malaria parasite belongs therefore unquestionably to Laveran, though the observations of Marchiafava and Celli have amplified by a good deal our knowledge of them; their merits, though considerable, are not commensurate to the credit they generally receive as compared with that accorded to Laveran; they have shown us, however, a good deal of the life history of the parasite, and have given it the name *hæmoplasmodium* or *plasmodium malariæ*. The researches of Golgi have made important additions as regards the life history and distribution of these parasites, and particularly as to their relation to the various forms of malarial fevers. We will follow in our description chiefly the very exhaustive observations made by Golgi and described by him in the 'Fortschritte der Medicin, 1889,' No. 3; but it ought to be mentioned at the outset that, according to Metschnikoff, Celli and Garnieri, the malaria parasite belongs really to the class of sporozoa amongst the protozoa, and, therefore, the name plasmodium malariæ introduced by Marchiafava and Celli is, according to Metschnikoff, incorrect.

Marchiafava and Celli[1] were the first to show that during the beginning of the febrile stage the parasite invades the red blood-corpuscles as small, globular, pale, homogeneous corpuscles measuring not more than a fifth to a seventh of the diameter of a red blood-corpuscle ; in this host the parasite performs active amœboid movements, hereby changing continually its shape ; but it gradually increases in size and consumes the substance of the red blood-corpuscle, leaving black pigment granules—iron-free melanin—in the disc. These pigment granules, as the parasite grows to the size of the original red blood disc, are contained within the body of the parasite, in which they appear uniformly distributed. When the disc of the red blood-corpuscle is entirely consumed by the growth of the parasite, this latter appears free in the blood plasma, its substance filled with the melanin granules ; some of these free parasites have cilia by which they move actively—these are the corpuscles seen by Laveran. Next, the pigment granules aggregate in the central part of the parasite and the peripheral, pale, homogeneous portion gradually undergoes a more or less regular mode of segmentation, in the course of which small globular particles or sporules become constricted off from the main body ; when this segmentation has been completed, the young gemmæ or sporules all disappear from the blood, so also the pigmented central parts, and are stored up in the spleen, liver, and bone marrow; this terminates one febrile attack. The next febrile attack is caused by the sporules again invading the blood-corpuscles of the general circulation, and therein undergoing the same series of changes as just described. So that each febrile stage comprises the invasion of the blood-corpuscles by the sporules, the germination, amœboid movement, and growth of these latter within and at the expense of the former, then the gemmation and segmentation of a new crop of sporules, and finally the disappearance of these from the general circulation. Golgi by his numerous researches was able to show that the various forms of malarial fever are due to various species of the parasite, at any rate that in the different forms of intermittent fever the time in which the parasite passes through all the above-mentioned phases of its development is different, and stands in a definite relation to the form of the fever. Thus, Golgi found that in the febris quartana, the parasite from its first appearance in the red blood-corpuscle, that is, from the onset of a febrile attack, through the complete segmentation of the full-grown parasite into the sporules, and to the disappearance of these from the general circulation, i.e. till the end of the febrile stage, requires three days, whereas in the febris tertiana it requires only two days. Besides, there are certain slight morphological differences between the parasite in the febris quartana and in that of the tertiana, as also differences in the mode of segmentation (*see* Plate XLII.). As to the parasite in the fever of irregular type, Golgi shows that also in this the time occupied for passing through its phases is irregular, either too rapid or too slow. The crescentic form of the parasites mentioned by Laveran and Marchiafava and Celli are present only in fever of irregular type, and are really an atypical form in the development of the parasite. So also the flagellate forms seen by Laveran are atypical forms.

Whether in these different forms we have really to deal with different species of the same group of parasites as Golgi inclines to think, or rather with differences in the life history of the same species caused by unknown conditions, e.g. individual person, different tissue, season, locality, &c., is not decided.

Canalis (' Studi della Infezione malariana,' Torino, 1889) studied the atypical forms of malarial fever, characterised by longer or shorter febrile intervals. He found in these cases an endoglobular form of the plasmodium malariæ, which has been signalised already by Golgi, viz. a crescentic form; but also here the commencement of the attack is characterised by the amœboid endoglobular forms, and the life cycle of the parasite becomes completed by its division into sporules.

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[1] 'Untersuchungen über die Malaria-Infection,' *Fortschritte d. Med.*, 1885, pp. 339 and 787.

Thomas Smith described in 1889 in the red blood discs of cattle affected with Texas fever the presence of parasites very similar to those occurring in human malarial fever, and the number of the infected blood discs is so enormous that it seems impossible to doubt that those parasites are the cause of the Texas fever; hence the bacilli described by Billings (*see* a former chapter) assume the character of saprophytic additions.

Danilewsky, Grassi and Feletti, Kruse, Pfeiffer, Celli and Sanfelice and others describe the occurrence of similar parasites in the red blood-corpuscles of a number of different animals, frogs and birds (*see* 'Fortschritte d. Med.,' Band IX., Nos. 12 and 13, 1891).

CHAPTER XXIV

TETANUS—RABIES AND HYDROPHOBIA

Carle and Rattone ('Giorn. dell. r. Accad. d. Med.' Torino, 1884) were the first to show that tetanus is a communicable disease. They succeeded in producing in rabbits typical tetanus, terminating fatally, by inoculating them with pus taken from the ulceration of a human being in whom tetanus had set in. Purulent exudation was taken in these rabbits from the place of inoculation and transferred to fresh rabbits, and here typical tetanus was again produced. In human tetanus the place of infection (produced in the skin of the hand or foot by a tainted splinter, earth, or other material) becomes marked as a purulent inflammation leading to ulceration; the tissue surrounding the ulceration is much infiltrated, and there is always hæmorrhage in it. After death the membranes of the brain and cord are found much injected, and so also the grey matter of the medulla and cord; occasionally there is a slight accumulation of red and white blood-corpuscles around the vessels.

Nicolaier ('Inaugural Diss.,' Göttingen, 1885) made the important discovery that earth taken from superficial layers of the soil is often capable of producing, when inoculated into the subcutaneous tissue of the mouse, rabbit, or guineapig, a local suppuration and hæmorrhagic effusion about the seat of inoculation, rapidly followed by typical tetanus and death. In that earth and in the pus and exudation of the seat of inoculation he demonstrated the constant presence of fine, straight bacilli, which he considered as the *tetanus bacilli.* The purulent matter containing these bacilli, inoculated into fresh mice, rabbits, or guineapigs, again produces tetanus. Rosenbach ('Archiv f. klin. Chirurgie,' Band XXXIV., 1886) showed that the same bacilli exist in the exudation at the place of infection in human tetanus. Hochsinger, Beumer and Peiper, Bonone, Shakespeare, Raun, and many others have confirmed the existence of these bacilli in tetanus, but no one of these succeeded in cultivating them in pure cultivations. Though numerous cultivations have been established, and tetanus has been produced in animals with them by the aid of foreign bodies—cotton wool, splinters, &c.—yet these cultivations were always in an impure state, until recently Kitisato ('Zeitschrift f. Hygiene,' Band VII., p. 225) succeeded in cultivating the tetanus bacillus of Nicolaier in pure cultivations (*see* Plate XXIX., fig. 37) and in producing tetanus with such pure cultures. Minimal doses inoculated into mice produced tetanus in twenty-four hours, death in two to three days. In the case of rats, rabbits, and guineapigs the dose had to be somewhat larger, 0·3–0·5 c.c. of broth culture. Rats and guineapigs are ill with tetanus even after twenty-four to thirty hours, rabbits not before two to three days. On *post-mortem* examination of such animals there is no suppuration at the seat of the inoculation, but only hyperæmia; hence the suppuration observed in other cases is not an essential feature, and in former experiments and in the case of human beings is probably only due to the presence of the foreign bodies themselves (earth, splinters, &c.) which were the vehicles of the tetanus bacilli; in the internal organs there is no definite change. In the organs there are no bacilli present, nor was it possible to produce tetanus in other animals by inoculating them with the cord, nerves, blood, or spleen of the animals dead of tetanus. In rabbits, Kitisato produced typical tetanus by injection of 0·5 cubic centimetre of broth culture of the tetanus bacillus into the vein of the ear. Also by injection of the culture into the dura mater after trephining, Kitisato produced typical tetanus; but neither in the brain, nor in the cord, nor in the blood or other viscera of these animals, could the tetanus bacilli be found.

The success of obtaining pure cultures of the tetanus bacilli was achieved by Kitisato by cultivating tetanus pus anaërobically; preliminarily to this he watched for the time when in ordinary cultures of the tetanus pus on serum or agar he found organisms amongst the different species of bacteria present, which, by their peculiar shape and by their containing a terminal thick spore, he recognised as the tetanus bacilli. By exposing such impure cultures for three-quarters of an hour to an hour in water at 80° C. all bacteria were killed except the spores. With material thus treated he made gelatine plate and tube cultures, but in such a way that the air was excluded by substituting for it an atmosphere of hydrogen gas, or by planting the bacilli in the depth of the gelatine. Under these anaërobic conditions he obtained pure cultures (Plate XXIX. fig. 37). In this figure the character of the cultures is well seen; the microscopic appearance of the bacilli is shown in fig. 102.

It appears, then, from these exact researches that the introduction of the tetanus bacilli under the skin is followed by the production by them of a chemical virus, which, as it is being produced at the seat of inoculation, is absorbed into the system and sets up the disease; but the bacilli themselves appear to remain limited to the seat of inoculation, and do not enter the blood or any other tissue, and therefore only the seat of the inoculation contains the infective principle, i.e. the bacilli; for this reason, the brain, cord, nerves, blood, and viscera have no power of producing infection.

Brieger has, as a matter of fact, isolated from the exudation at the seat of infection in human tetanus a toxic principle, *tetanin*, the injection of which produces tetanus symptoms in animals; and Kitisato showed this held good also for the tetanin obtained from the cultures of the tetanus bacilli.

Behring and Kitisato ('Zeitschrift für Hygiene,' X.) showed that the blood of rabbit (previously made insusceptible to tetanus) injected into a mouse (otherwise susceptible to tetanus) neutralises in this latter the action of the tetanus bacillus.

Vaillard and Vincent ('La Semaine médicale,' No. 51, 1890) have published strong chemical evidence to show that *tetanin* is neither an albumose nor an alkaloid, but is related in its chemical characters to snake poison.

Buchner and also Kitt ('Centralb. f. Bact. und Parasit.,' VII., No. 10) have also succeeded in obtaining pure cultures of the tetanus bacilli. Their characters agree with those stated by Kitisato, except that Kitt found that the tetanus bacilli obtained from the horse liquefy solid blood serum. Kitt points out that in the tetanus of horses—a not uncommon disease—the pus taken from the local abscess, generally about the hoof, when inoculated into mice and horses, produces without fail fatal tetanus. Kitt has found that such pus dried even for four months, when inoculated in minimal doses, has still virulent action; this fact is easily explained by remembering that the tetanus bacilli present in the pus and in the local exudation contain spores.

In his 'Experimental Researches on the Poison of Tetanus' ('Zeitschr. f. Hygiene,' X., 2) Kitisato gives a full account of the influence of light, heat, drying, and of various chemical substances on the tetanus poison.

Tizzoni and Cattani, in a series of memoirs, demonstrated the means by which animals, naturally possessed of slight or great susceptibility, can be made altogether insusceptible to tetanus; further, the blood serum of animals, made previously insusceptible, when injected into animals possesses a decided antitoxic action. They have isolated from such blood serum this substance—the tetanus antitoxin—by precipitating with alcohol, drying in vacuo, and dissolving in water. In four cases of human tetanus, the disease was arrested by the injection of the antitoxin of Tizzoni, and the patients recovered ('Centralbl. f. Bact. und Parasit.,' Band X., No. 24, p. 785).

RABIES OR HYDROPHOBIA

This disease, which always terminates fatally, is common to man and carnivorous animals: to man it is invariably transmitted from a rabid animal—dog, wolf, cat. Dogs are the common breeders of this malady, next come wolves. In Russia especially this species yields a considerable number of cases. In India, rabies amongst dogs is common, amongst jackals not uncommon. Cats when bitten or infected by rabid dogs become affected with rabies; cows, horses, asses, sheep, and deer are susceptible to rabies, and occasionally become affected by it owing to the bite from a rabid dog; rabbits and monkeys have been experimentally proved by Pasteur to be easily susceptible to the disease.

The pathology of the disease in man does not offer striking changes; and they are chiefly limited to the place of infection, i.e. the bite of a rabid animal. The wound with the onset of the disease is tumid, injected, and painful—in fact, it is this change in the place of infection which indicates the onset of the disease, previous to the actual outbreak of the disease. There is no symptom observed at the place of inoculation during incubation. After death the most noteworthy pathological changes refer to the salivary glands, the stomach, and the central nervous system. In all these organs we find general congestion: in the salivary glands the gland alveoli are in a state of exhaustive secretion; in the parotid the gland cells of the alveoli are swollen and opaque, and the lumen of the alveoli almost obliterated; in the submaxillary gland the number of mucous alveoli is greatly in excess of what is the case in the normal gland; the cells of all mucous alveoli are in a state of extreme mucous change; and at the same time there are present numerous round cells in the interalveolar and interlobular connective tissue. The most noteworthy changes are found in the central nervous system. Besides the general congestion of the blood-vessels, many vessels of the grey matter are surrounded by leucocytes and red blood-corpuscles, almost forming in some places special sheaths of white and red corpuscles in the perivascular lymph spaces surrounding the blood-vessels; also in the lymph spaces surrounding the ganglion cells, i.e. the pericellular lymph spaces, a few leucocytes are contained. In the central nervous system the accumulation of cells in the perivascular and pericellular lymph spaces is very marked. In animals (dogs, rabbits) the mucous and serous coats of the stomach, particularly the former, show petechiæ and extensive patches of hæmorrhages; in the dog affected naturally with rabies—street rabies—the submaxillary glands are swollen, congested, and the mucous cells lining the alveoli enlarged and full of mucus.

That rabies is a communicable disease, transmitted from animal to animal, and from animal to man by the bite of a rabid animal, has been well recognised by physicians and veterinarians, though the spontaneous origin of the disease has been occasionally asserted; but not until Pasteur's observations was it proved that the disease is experimentally transmissible from animal to animal. The experimental proof furnished by Pasteur has been the starting point for a more precise understanding of the malady, till then shrouded in a good deal of mystery; it has further been the beginning of an entirely new era in the prophylaxis against this terrible disorder, a prophylaxis, the value of which can now no longer be doubted. The discoveries by Pasteur of the nature of, and protective inoculation against, this malady may justly be regarded as some of those few discoveries which mark a new epoch in scientific medicine. Before Pasteur's researches the experimental production of rabies was practically unknown; Pasteur showed that the central nervous system of an animal or human being dead of rabies contains the virus of the disease, and that if a portion of such central nervous system—the cord in the fresh state—be injected subdurally into a susceptible animal, this latter becomes, with absolute certainty, the subject of the malady, the period intervening between the injection and the actual outbreak of the disease differing with the material used and with the animal into which it is injected. This discovery at once proved of immense diagnostic value, since it was now possible to determine whether in a given case the human being or the animal, as the case may be, had really died from hydrophobia. This proof was of especial importance in those cases in which the pathology and symptoms of the antecedent disease had not been typical, and where the diagnosis of rabies could not be formed with anything like certainty from the clinical and pathological point of view, and such cases, as is well known, are not by any means rare. With Pasteur's discovery it became easy to decide the question: the fresh spinal cord (a portion emulsified in water or broth) injected subdurally into a rabbit produces rabies with absolute certainty, if the human being or animal from whom that cord was taken had really died from hydrophobia. This is a considerable step in advance of all previous knowledge, and in itself represents a definite landmark.

We cannot do better than quote *in extenso* from the Report of the English Commission on Pasteur's Researches on Hydrophobia (consisting of Sir James Paget, chairman; Dr. T. Lauder Brunton, Dr. G. Fleming, Sir Joseph Lister, Sir R. Quain, Sir Henry Roscoe, Professor Burdon-Sanderson, and Professor V. Horsley, secretary). A *résumé* of experiments made in this direction by Professor Horsley is here reproduced from that report, pp. 1 and 2:

> 'Through the kindness of M. Pasteur two rabbits inoculated by him were placed at the disposal of the committee on May 5, 1886, and were conveyed within twenty-four hours safely to the Brown Institution, where the experiments were carried out by Mr. Horsley.
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> 'In these two rabbits the first symptoms of rabies appeared on May 11 and 12, and the disease followed exactly the course described by M. Pasteur.
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> 'At first the animals appeared dull, but continued to take food readily until symptoms of paralysis appeared. The first of these symptoms was commencing paralysis of motion

of the hind legs, not accompanied by any loss of sensibility. The paralysis soon extended to the muscles of the forelegs and later to those of the head, and the animals died comatose.

'After *post-mortem* examination, portions of the spinal cord of each of these rabbits were crushed according to M. Pasteur's method in sterilised broth, and the liquid so obtained was injected beneath the dura mater into four rabbits and the same number of dogs, all being first rendered insensible with chloroform or ether.

'Of the four rabbits so inoculated, the first two showed the first symptoms seven days after the inoculation, the third and fourth on the sixth day. The symptoms as well as the incubation period exhibited by these rabbits were exactly the same as were observed in those brought from M. Pasteur's laboratory. Careful notes and photographs were taken in the case of all the animals, in order that the constant and specific nature of the disease might be demonstrated by observations during life and after death. It was also observed that during the incubation period the temperature of the body remained normal, that is, about 39·4° C. With the first definite symptom the temperature rose to about 40·4° C., which is the temperature usually observed during the first day of the obvious illness. By the next day it began to fall, and on the third day, after the appearance of the first symptom, it averaged 37·5° C. On the last day it was always below normal, and on one occasion fell before death to 24° C. The animals did not appear to suffer any pain whatever in the course of the disease. They were free from the spasms which, in the earlier stages of the malady in man, form so painful a feature of the disease, and, indeed, the disease in them resembled throughout that rapidly fatal but painless disease of man known as acute ascending paralysis.[1]

'The *post-mortem* appearances in the rabbits were remarkably uniform. As a rule, nothing abnormal, save congestion, presented itself either in the brain, spinal cord, heart, blood-vessels, or serous membranes. The larynx, pharynx and, more especially, the epiglottis and the root of the tongue were frequently intensely congested. The lung showed almost invariably capillary congestion, and sometimes small patches resembling bronchopneumonia were observed. The mucous membrane of the stomach was very markedly congested, and there were at its cardiac extremity numerous hæmorrhages.[1] The constancy of these appearances was most remarkable, and corresponded in every particular with those subsequently observed in rabbits which had died of rabies from the bite of rabid dogs.

'Of the four dogs inoculated, the first showed on the eighth day after inoculation an alteration in the voice and commencing excitement; on the following day the excitement became excessive, and the bark was quite characteristic; on the eleventh day the dog was aggressive, notwithstanding slight paralysis of the legs; on the twelfth day the paralysis had increased; and on the next day there was complete paralysis and coma, and death occurred on the fifth day after the onset of the symptoms.

'The second dog showed the first symptom on the ninth day after inoculation, when it was very dull and partially paralysed; its bark was characteristic. Next day the paralysis was almost complete, and on the twelfth day the animal died. This was therefore a case of the rapid paralytic form; whilst in the first dog the disease was of the ordinary furious form of rabies terminating in paralysis.

'The third dog showed the first symptom on the ninth day after inoculation, and from that time became gradually paralysed, and died on the sixteenth day.

'The fourth dog showed the first symptom in from eight to nine days after inoculation, and during the first day was extremely aggressive; on the two following days the characteristic bark was observed; and on the twelfth day there was paralysis of the hind legs; it died on the thirteenth day. Thus the furious form and the paralytic or dumb form of rabies were represented in equal numbers, whereas, in the usual mode of infection by biting, the former is more prevalent.

'The *post-mortem* appearances were as follows: The brain and central nervous system were in some of the dogs the seat of considerable congestion, in others these organs appeared normal. The serous membranes were perfectly normal; the larynx especially and, sometimes, the pharynx were congested; the lungs always congested, especially in the lower lobes; the heart normal; the blood usually fluid, occasionally with *post-mortem* clots; the stomach was always found to contain foreign bodies, such as straw; and its mucous membrane was congested, frequently showing numerous hæmorrhages; the small intestine was always empty, and the large glandular organs showed venous congestion.

'For the purpose of exact comparison of the disease just described with that produced when rabies is communicated to the rabbit in the ordinary way, some rabbits previously narcotised with ether were caused to be bitten by rabid dogs of the streets, or were inoculated by trephining with material obtained from the spinal cord of dogs or other animals which had died of rabies, and in one instance from that of a man who had died with hydrophobia.

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[1] 'In some, signs of *post-mortem* digestion were found.'

'Four series of experiments were made in which rabbits were bitten by rabid dogs from the streets. In one of them the dog by which the rabbit was bitten exhibited the dumb form, in others the furious form of the disease. In each series excepting the first a large proportion of the rabbits died; the symptoms presenting themselves in these cases were identical with those observed in the rabbits inoculated from M. Pasteur's virus, but the duration of the symptoms was usually longer. As has been stated, rabbits inoculated by M. Pasteur's virus rarely show symptoms during more than three days before death, whereas the rabbits bitten by rabid dogs from the streets often live for a week after the appearance of the first symptoms.

'The *post-mortem* appearances in the rabbits dying after having been bitten by rabid dogs of the streets were the same as those already described in rabbits inoculated with the virus from M. Pasteur's rabbits.

'In the case of rabbits inoculated by trephining with the virus from animals dying of rabies of the streets, the incubation period was from fourteen to twenty-one days. In all cases the symptoms were similar to those produced by M. Pasteur's virus, and those of rabbits bitten by rabid dogs from the streets, but in the prolongation of the disease approached more closely in character to the latter.

'The results of these experiments confirm several of the chief observations made by M. Pasteur, especially—

'1. That the virus of rabies may certainly be obtained from the spinal cords of rabbits and other animals that have died of that disease.

'2. That, thus obtained, the virus may be transmitted by inoculation through a succession of animals without any essential alteration in the nature, though there may be some modifications of the form, of the disease produced by it.

'3. That, in transmission through rabbits, the disease is rendered more intense, both the period of incubation and the duration of life after the appearance of symptoms of infection being shortened.

'4. That, in different cases, the disease may be manifested either in the form called dumb or paralytic rabies, which is usual in rabbits; or in the furious form usual in dogs; or in forms intermediate between or combining both of these, but that in all it is true rabies.

'5. The period of incubation and the intensity of the symptoms may vary according to the method in which the virus is introduced, the age and strength of the animal, and some other circumstances; but, however variable in its intensity, the essential characters of the disease are still maintained.

'The certainty that the virus of rabies can thus be transmitted without essential change made it desirable, in the next place, to ascertain whether, as M. Pasteur states, it can be so attenuated that it may be inoculated without risk to life, and whether animals thus inoculated are thus made safe from rabies.'

The next point ascertained by M. Pasteur was the possibility of preventive or protective inoculation. The spinal cord of an animal dead of natural or experimental rabies, and subjected to drying, was found to lose virulence in the proportion of its drying, so that according to the period of drying, strong, medium, or weak virus may be obtained, the injection of the first producing rabies, and the latter producing slight or no appreciable result.

Animals bitten by a rabid dog, and soon after, i.e. in the early part of the incubation period, subjected to inoculation with the above-mentioned virus, can be prevented from developing the disease, the inoculation being carried out on repeated occasions, starting with virus of lesser virulence, i.e. from a cord dried longer, and following with injection of a cord of increasing virulence, and finishing with inoculation of a cord of intensive virulence, such as if at once used would unfailingly produce fatal rabies. Under this mode of treatment the animal does not contract the disease, and the effect of the original infection, i.e. by the bite of a rabid dog, is prevented. In a like manner intact dogs treated in this way and then subjected to infection with rabic virus (either by the bite of a rabid dog or by artificial injection with virulent material), prove themselves completely *protected*. To test this important proposition the English Commission made the following experiments (*ibid.* pp. 2 and 3):—

'Six dogs were "protected" by injecting subcutaneously the emulsions of spinal cords of rabbits which had died of rabies, beginning with that of a cord which had been dried for fourteen days and, on each following day, using that of a cord which had been dried for one day less, till at last that from a fresh cord was used.

'None of these dogs suffered from the injections; and when they were completed, the six dogs thus "protected," and two others unprotected, and some rabbits unprotected, were made insensible with ether, and were then bitten by rabid dogs, or by a rabid cat, on an exposed part.

'A "protected" dog, No. 1, was bitten on July 8, 1886, by a dog which was paralytically rabid. It remains perfectly well.

'An "unprotected" dog, No. 1, was bitten a few minutes afterwards by the same rabid dog, and died paralytically rabid.

'A "protected" dog, No. 2, was bitten on November 6, 1886, by a dog which was furiously rabid; it remains well. At the same time, four "unprotected" rabbits were bitten by the same rabid dog, and of these two died of rabies in the usual form (i.e. 50 per cent. of animals bitten).

'The same result followed with the "protected" dog, No. 3, and the "unprotected" rabbits, bitten at the same time. The dog still lives; the rabbits died of rabies.

'The "protected" dogs, Nos. 4 and 5, were bitten on January 20, 1887, by a furiously rabid dog; and on the same day the "unprotected" dog, No. 2, and three "unprotected" rabbits were bitten by the same dog. The protected dogs remain well; the unprotected dog and two rabbits died with rabies (i.e. 75 per cent. of the animals bitten).

'The "protected" dog, No. 6, was bitten on three different occasions by a furiously rabid cat on September 7, 1886; by a furiously rabid dog on October 7, 1886; and by another furiously rabid dog on November 6, 1886. It died ten weeks after being bitten for the third time, but not of rabies. It had been suffering with diffuse eczema during the whole of the time that it was under observation, and it died of this. At the *post-mortem* examination, no indication of rabies was found; and two rabbits inoculated by trephining with the crushed spinal cord showed no sign of rabies, either during life or when they were killed several months afterwards, in any appearance after death. It was thus made certain that the dog was not rabid.'

In these experiments it was found that the cord of a rabbit dead of the disease, dried at 20° C. over caustic potash for fourteen days, is the weakest degree of virulence to be employed; dried for one day the strongest; longer drying than fourteen days almost destroys the virus. Pasteur then proceeded to use this method for preventive inoculation of human beings bitten by rabid dogs ('Report,' p. 3, and pp. 4, 5, and 6).

'The evidence that an animal may thus, by progressive inoculations, be protected from rabies suggested to M. Pasteur that if any animal or any person, though unprotected, were bitten by a rabid dog, the fatal influence of the virus might be prevented[1] by a timely series of similar progressive inoculations. He has accordingly, in the institution established by him in Paris, thus inoculated a very arge number of persons believed to have been bitten by rabid animals; and we have endeavoured to ascertain with what amount of success he has done so.

'The question might be answered with numerical accuracy if it were possible to ascertain the relative numbers of cases of hydrophobia occurring among persons of whom, after being similarly bitten by really rabid animals, some were and some were not inoculated. But an accurate numerical estimate of this kind is not possible.

'1. It is often difficult, and sometimes impossible, to ascertain whether the animals by which people were bitten, and which were believed to be rabid, were really so. They may have escaped, or may have been killed at once, or may have been observed by none but persons quite incompetent to judge of their condition.

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[1] 'The terms referring to "preventive" treatment will be used for that designed to prevent the occurrence of the disease in one already infected; those referring to "protective" treatment for that designed to protect a man or an animal from the risk of becoming infected. And it may be well to state that, though the usual custom is followed of employing the name of "hydrophobia" for the disease in men, and of "rabies" for that in animals, they are really the same disease.'

'2. The probability of hydrophobia occurring in persons bitten by dogs that were certainly rabid depends very much on the number and character of the bites; whether they are on the face or hands or other naked parts, or if they have been inflicted on parts covered with clothes, their effects may depend on the texture of the clothes and the extent to which they are torn; and in all cases the amount of bleeding from the wounds may affect the probability of absorption of virus.

'3. In all cases, the probability of infection from bites may be affected by speedy cauterising or excision of the wounded parts, or by various washings or other methods of treatment.

'4. The bites of different species of animals, and even of different dogs, are probably, for various reasons, unequally dangerous. Last year, at Deptford, five children were bitten by one dog and all died; in other cases a dog is said to have bitten twenty persons, of whom only one died. And it is certain that the bites of rabid wolves, and probably that those of rabid cats, are far more dangerous than those of rabid dogs.

'The amount of uncertainty due to these and other causes may be expressed by the fact that the percentage of deaths among persons who have been bitten by dogs believed to have been rabid, and who have not been inoculated, or otherwise treated, has been, in some groups of cases, estimated at the rate of only 5 per cent., in others at 60 per cent., and in others at various intermediate rates. The mortality from the bites of rabid wolves, also, has been, in different instances, estimated at from 30 to 95 per cent.

'To ascertain, as far as possible, the influence of these sources of fallacy in cases inoculated by M. Pasteur, the members of the committee who went to Paris requested him to enable them to investigate, by personal inquiry, the cases of some of those who had been treated by him. He at once, and very courteously, assented, and the names of ninety persons were taken from his note-books. No selection was made, except that the names were taken from his earliest cases, in which the periods since inoculation were longest, and from those of persons living within reach in Paris, Lyons, and St. Etienne.

'The notes made on the spot concerning all these cases are given in the Appendix (p. 3), and they include, as far as was possible, the evidence whether the dogs deemed rabid were really so, the situation and kind of bites, the immediate treatment of them, the statements of medical practitioners and veterinary surgeons to whom any useful facts were known.

'Among the ninety cases there were twenty-four in which the patients were bitten on naked parts by undoubtedly rabid dogs, and the wounds were not cauterised or treated in any way likely to have prevented the action of the virus; there were thirty-one in which there was no clear evidence that the dog was rabid; others in which the bite, though inflicted by undoubtedly rabid animals, having been through clothes, may thus have been rendered harmless. Among these, therefore, it is probable that, even if they had not been inoculated, few would have died. Still, the results observed in the total of the ninety cases may justly be compared with those observed in large numbers of cases similar to these as regards the uncertainties of infection, but not inoculated. The estimates published as to the mortalities in such unassorted cases are, as we have said, widely various. We believe that among the ninety persons, including the twenty-four bitten on naked parts, not less than eight would have died if they had not been inoculated. At the time of the inquiry, in April and May 1886, which was at least eighteen weeks since the treatment of the bites, not one had shown any signs of hydrophobia, nor has any one of them since died of that disease.

'Thus, the personal investigation of M. Pasteur's cases by members of the committee was, so far as it went, entirely satisfactory, and convinced them of the perfect accuracy of his records.

'After the first few months in which M. Pasteur practised his treatment, he was occasionally obliged, in order to quiet fears, to inoculate persons who believed that they had been bitten by rabid animals, but could give no satisfactory evidence of it. It might, therefore, be deemed unjust to estimate the total value of his treatment in the whole of his cases as being more than is represented by the difference between the rate of mortality observed in them and the lowest rate observed in any large number of cases not inoculated. This lowest rate may be taken at 5 per cent. Between October 1885 and the end of December 1886 M. Pasteur inoculated 2,682 persons, including 127 who went from this country (*see* Appendix, p. 19). Of the whole number, at the rate of 5 per cent., at least 130 should have died. At the end of 1886 the number of deaths stated by M. Vulpian, speaking for M. Pasteur, was thirty-one, including seven bitten by wolves, in three of whom the symptoms of hydrophobia appeared while they were under treatment, and before the series of inoculations were complete. Since 1886 two more of those inoculated in that year have died of hydrophobia.

'The number of deaths assigned by those who have sought to prove the inutility of M. Pasteur's treatment is, as nearly as we can ascertain, forty out of the 2,682; and in this number are included the seven deaths from bites by wolves, and probably not less than four in which it is doubtful whether the deaths were due to hydrophobia or to some other disease. Making fair allowance for uncertainties and for questions which cannot now be settled, we believe it sure that, excluding the deaths after bites by rabid wolves, the proportion of deaths in the 2,634 persons bitten by other animals was between 1 and 1·2 per cent.; a proportion far lower than the lowest estimated among those not submitted to M. Pasteur's treatment, and showing, even on this lowest estimate, the saving of not less than 100 lives.

'The evidence of the utility of M. Pasteur's method indicated by these numbers is confirmed by the results obtained in certain groups of his cases.

'Of 233 persons bitten by animals in which rabies was proved, either by inoculation from their spinal cords, or by the occurrence of rabies in other animals or in persons bitten by them, only four died. Without inoculation it would have been expected that at least forty would have died.

'Among 186 bitten on the head or face by animals in which rabies was proved by experimental inoculations or was observed by veterinary surgeons, only nine died, instead of at least forty; and of the forty-eight bitten by rabid wolves only nine died, while, without the preventive treatment, the mortality, according to the most probable estimates yet made, would have been nearly thirty.

'Between the end of last December and the end of March, M. Pasteur inoculated 509 persons bitten by animals proved to have been rabid, either by inoculation with their spinal cords, or by the deaths of some of those bitten by them, or as certified by veterinary surgeons. Only two have died, and one of these was bitten by a wolf a month before inoculation, and died after only three days' treatment. If we omit half of the cases as being too recent, the other 250 have had a mortality of less than 1 per cent., instead of 20 or 30 per cent.

'It has been objected that the number treated by M. Pasteur, which, from October 1885 to the end of 1886, included 1,929 French and Algerians, was much greater than could reasonably be supposed to have been bitten by rabid animals. But there had hitherto been no careful registration of such cases, and the numbers that have occurred in the present year are not less than in the same part of last year, when the alarm about hydrophobia was greatest.

'From the evidence of all these facts, we think it certain that the inoculations practised by M. Pasteur on persons bitten by rabid animals have prevented the occurrence of hydrophobia in a large proportion of those who, if they had not been so inoculated, would have died of that disease. And we believe that the value of his discovery will be found much greater than can be estimated by its present utility, for it shows that it may become possible to avert by inoculation, even after infection, other diseases besides hydrophobia. Some have, indeed, thought it possible to avert small-pox by vaccinating those very recently exposed to its infection, but the evidence of this is, at the best, inconclusive; and M. Pasteur's may justly be deemed the first proved method of overtaking and suppressing by inoculation a process of specific infection. His researches have also added very largely to the knowledge of the pathology of hydrophobia and have supplied what is of the highest practical value, namely, a sure means of determining whether an animal, which has died under suspicion of rabies, were really affected with that disease or not.

'The question has been raised whether M. Pasteur's treatment can be submitted to without danger to health or life, and in answering it, it is necessary to refer to two different methods of inoculation which he has practised, and which are fully described in the Appendix (p. 21).

'In the first, which may be called the ordinary method, and which has been employed in the very large majority of cases, the preventive material obtained from the spinal cord of rabbits that have died of rabies derived originally from rabid dogs is injected under the skin once a day, for ten days, in gradually increasing strengths.

'In the second or intensive method, *méthode intensive*, which M. Pasteur adopted for the treatment of cases deemed especially urgent, on account either of the number and position of the bites or of the long time since their infliction, the injections, gradually increasing in strength, were usually made three times on each of the first three days, then once daily for a week, and then in different degrees of frequency for some days more. The highest strength of the injections used in this method was greater than the highest used in the ordinary method, and was such as, if used at first and without the previous injections of less strength, would certainly produce rabies.

'By the first or ordinary method, there is no evidence or probability that anyone has been in danger of dying, or has in any degree suffered in health even for any short time. But after the intensive method, deaths have occurred under conditions which have suggested that they were due to the inoculations rather than to the infection from the rabid animal.

'There is ample reason to believe that, in many of the most urgent cases, the intensive method was more efficacious than the ordinary method would have been. Thus, M. Pasteur mentions that, of nineteen Russians bitten by rabid wolves, three treated by the ordinary method died, and the remaining sixteen, treated by the intensive method, survived; and he contrasts the cases of six children, severely bitten on the face, who died after the ordinary treatment with those of ten similarly bitten children who were treated by the intensive method, and of whom none died; and M. Vulpian reports that of 186 persons badly bitten by animals that were most probably rabid, fifty treated by the intensive method survived, and of the remaining 136 treated by the ordinary method nine died.'

Although several observers have mentioned that they have identified the microbe of hydrophobia in the form of a coccus, this has not been as yet confirmed, and the nature of the virus is still undiscovered.

As to Pasteur's views on the nature of the rabic virus and the methods of preventive inoculation, we quote here from the 'Report of the English Pasteur Commission,' pp. 21 and 22:—

'M. Pasteur believes that the virus of rabies is a living micro-organism, and that, like some others, it produces in the tissues it invades an excretory substance by which, when present in sufficient quantity, its own development and increase are checked, as are those of the yeast ferment by the alcohol produced in the vinous fermentation. In accordance with this theory, he thinks that the spinal cords of animals that have died of rabies contain both the virus and this excretory substance, which, practically, may be deemed its antidote. He believes, therefore, that by injections of an emulsion from such spinal cords into the systems of animals bitten or inoculated with the virus of rabies, the antidote may be able, during the period of incubation, to arrest and prevent the fatal influence of the virus. But, in order to avoid the possibility of injecting a still potent virus, M. Pasteur holds that the virus in the spinal cord must be weakened by drying the cord in a pure and dry atmosphere at a temperature of 20° C., in which drying the efficiency of the antidote may be reduced to a much less extent than the potency of the virus. By such drying this potency may be so reduced that an emulsion of the dried spinal cord may be injected without any risk of producing rabies, and this risk is in no measure increased by the daily injections of emulsions from cords dried during a gradually less number of days, and which, though more virulent than those first used, still contain a larger proportion of the antidote than of the virus.

'In accordance with this theory, the method of the preventive injections first used by M. Pasteur was adjusted in the following manner:—

Days of Inoculation	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Days during which the spinal cord had been dried	14	13	12	11	10	9	8	7	6	5

'In consequence of some deaths among those who had been thus treated, M. Pasteur deemed it necessary, in cases of very severe bites, and of persons bitten long before the treatment could be commenced, to increase the intensity of the treatment by more speedily increasing the strength of the injections, by more frequent repetitions of them, and by using on certain days spinal cords dried during only three, two, and one day. Thus in September and October 1886 he adopted the following formula:—

Days of Inoculation	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
Days' drying of the cords . .	14, 13, 12	11, 10, 9	8, 7	6, 5	4, 3	2	1	6, 5	4, 3	2	1

'In very severe and perilous cases this course was repeated even three or four times. It was distinguished as the *méthode intensive*, and among such severe cases it was followed by a marked diminution of mortality. But when it appeared possible that it might be dangerous, M. Pasteur changed it for that which he now uses, and which may be thus represented:—

Days of Inoculation	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th	12th	13th	14th	15th
Days' drying of the cords .	14, 13	12, 11	11, 10	10, 10	9, 9	9	8	8	8	7	7	7	6	6	5

'The material for injection is prepared by crushing portions of the dried spinal cord, and diffusing them in sterilised broth free from all risk of putrefaction, decomposition, or any change due to the presence of other micro-organisms; and the injection is made with syringes through fine tubular needles into the subcutaneous tissue.

'For transmission of rabies through rabbits, in order to obtain the spinal cords required for its prevention in other animals, injections of virus of highest intensity are made through minute holes in the skull into the space under the dura mater or fibrous covering of the brain.

'The materials for the protective inoculations are prepared in the same manner as those for the preventive, from spinal cords dried from ten days to one day.'

CHAPTER XXV

GLANDERS AND FARCY—SYPHILIS—RHINOSCLEROMA

Glanders is a subacute or chronic infectious disease of the nasal mucous membrane, respiratory organs, and skin in the horse, leading to death; when the seat of the pathological process is localised in the skin it is spoken of as farcy, but both are the same disease. Glanders is communicable to the ass, mule, and man, and leads sooner or later to death; in man it is generally acute, though also in horses it sometimes assumes the acute form. The disease consists of nodular deposits in the mucous membrane of the nose, the septum particularly. The young nodules are grey, deep seated, not larger than a hemp seed or millet seed, and surrounded by congested mucous membrane. Microscopically they consist of an aggregation of round cells of various sizes, and in this phase are in structure not easily distinguishable from young tubercles; they soon enlarge, their central parts becoming purulent, and hereby small abscesses are formed which open on the free surface. Where close together they become confluent and form large ulcers, irregular in shape, with a grey purulent depressed centre, and a raised, injected border, the tissue around them being congested and infiltrated. The mucous membrane of the septum becomes riddled with abscesses, and soon also the cervical lymph glands become swollen and purulent; the process gradually extends to the pharynx, larynx, trachea, and lungs. In this latter numerous nodules appear, at first small (hemp seed) and grey, but gradually enlarging and transforming into abscesses situated in the depth of the lung, as well as on the surface. Neighbouring nodules and abscesses become confluent, and in this way extensive cavities are formed, whose purulent contents discharge themselves into the bronchi, the tissue around them being much congested and infiltrated. In the skin, the cutis and subcutaneous tissue are the seat of the nodules; here also they are at first small and grey, and represent round cell aggregations, which gradually enlarge into the congested and infiltrated surrounding tissue; purulent change is also here the natural result, and by opening on the free surface they form open sores discharging a little pus; the centre is depressed, covered with greyish purulent matter; the periphery is raised and much infiltrated.

The general mode of infection seems to be that of inoculation. It appears to be doubtful whether the direct transmission of the glanders material on to the intact nasal mucous membrane can produce infection, since such a mode yields experimentally no result; but cutaneous and subcutaneous inoculation in horses and asses is always followed by the characteristic disease of the nasal mucous membrane.

Horses and asses are very susceptible; of carnivorous animals, glanders has been observed in feline animals (lions and tigers fed on flesh of glandered horses); cats, dogs, and sheep are only very slightly susceptible, but in goats, glanders has been observed; in cattle, glanders is unknown. Rodents are easily infected by inoculation (*see* the experiments of Löffler and Schütz).

In man, glanders occurs after infection from the horse, generally through a cutaneous wound; it generally runs an acute course, characterised by the appearance of purulent infiltration about the seat of infection of the skin, particularly the muscular tissue, then in the lung and respiratory mucous membrane; metastatic purulent infiltration occurs also in the joints, the liver, spleen, kidneys, and testes. Löffler and Schütz, as also Israel, were the first to show that in glanders the deposits constantly contain a definite species of bacilli; they occur generally isolated, and in small groups between, and also enclosed in, the cells of the nodules: they are more numerous in the nodules which have not become purulent; after the nodules have become purulent the number of the bacilli in them diminishes. The bacilli are fine rods, of about the same size as tubercle bacilli, but a little thicker, rounded at their ends, straight, or sometimes more or less curved; this latter is especially noticed when they lie in groups; their substance is either homogeneous, or, like that of the tubercle bacilli, shows segregation of the protoplasm into granules within the sheath. The bacilli stain best in alkaline methylene blue and subsequent washing in acidulated water (acetic acid 1 per cent.); also in alkaline fuchsin of Ehrlich, or in gentian violet aniline water. The bacilli are easily cultivated at 35–38° C. on blood serum, agar mixture, and potato. On boiled potato at 35° C., they form a characteristic brownish yellow amber-coloured sticky film. On solid blood serum at 37° C., after three days, one notices small translucent droplets slightly projecting over the general surface. These are the youngest colonies. On agar culture the colonies are also translucent greyish droplets, gradually flattening and becoming dark in the centre (Plate XXXI., fig. 50).

There is no difficulty in obtaining good cultures in the ordinary beef broth peptone gelatine kept at 20–21° C., as also on potato at this temperature. They form on ordinary gelatine whitish-grey, flat, round, disc-shaped colonies. The gelatine is only very slowly liquefied.

According to Raskina the glanders bacilli grow also at 18–20° C., on gelatine, milk, serum, and white of egg. Kranzfeldt grew them also on glycerine agar mixture.

Löffler and Schütz proved that the artificial cultivations inoculated into horses and asses produced typical glanders. On most white mice the bacilli do not act, nor does fresh glanders material directly taken from the horse;[1] wild mice (field mice), however, are very susceptible to inoculation with the cultures; they die within eight days, and their spleen and liver are riddled with yellowish-grey minute nodules containing abundant glanders bacilli. In the rabbit, subcutaneous inoculation produces generally a positive result; in most cases, however, only a local abscess is formed which leads to a rapidly healing sore. In guineapigs, both the fresh glanders material and the culture produce a characteristic disease: on the third or fourth day a sore is found at the seat of inoculation, which soon involves the nearest lymphatics, these being found swollen and congested; further, the testes or ovaries become much swollen, congested, and the seat of minute glanders nodules; so does the skin and the nasal mucous membrane, leading to purulent infiltration and, after the discharge of the pus, to ulceration. The spleen contains white nodules. The glanders bacilli are everywhere present in the deposits.

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[1] H. Leo (*Zeitschrift f. Hygiene*, VII., 3) succeeded in giving glanders to white mice after feeding them for days with phloridzine, whereby their tissues contained much sugar.

Glanders bacilli of cultures are killed by prolonged drying (in about fourteen days); the glanders material taken direct from the horse becomes innocuous after a few days' drying: these facts seem to indicate that the bacilli do not form spores. With this the observation of Löffler also agrees, that the cultures of the bacilli die after a few months, and Cardéal and Malet found that putrefaction destroys the bacilli, though only after many days. Löffler studied also the resistance of the bacilli to heat, and he found that, for instance, ten minutes' heating to 55° C. completely killed the bacilli of the cultures; in this respect the glanders bacilli are even less resistant than many other non-spore bearing bacilli. Further, Löffler found that perchloride of mercury (1:5,000) kills the bacilli in two minutes, and carbolic acid (3 to 5 per cent.) in five minutes. All these facts strongly indicate that no spore formation takes place.

Within quite recent times it has been shown by a series of observations, carried out by a number of workers,[1] that chemical substances present in the artificial cultures of the glanders bacilli (Malleïn) injected into horses produce a definite reaction, viz., a decided rise of temperature, if the animals are affected with glanders; but no reaction follows in healthy horses. So that in doubtful cases the injection of the Malleïn determines the diagnosis. The Malleïn is prepared in the same way as Koch's tuberculin (*see* below), and is a further instance of the vast importance of the study of the chemistry of pathogenic bacteria.

The literature on the subject of the glanders bacilli is very copious, but the following are the chief works:—

Löffler and Schütz: 'Deutsche med. Wochenschrift,' 1882, No. 52.
Israel: 'Berliner klin. Woch.,' 1883, No. 11.
Kitt: 'Jahreschr. der. kgl. Thierarznei in München,' 1883–4.
Weichselbaum: 'Wiener med. Wochenschrift,' 1885, Nos. 21–24.
Löffler: 'Arbeiten aus d. kais. Gesundheitsamte,' 1886.
Raskina: 'Zeitschrift f. wiss. Mikroskopie,' IV. 1887.
Kranzfeldt: 'Centralbl. f. Bacteriologie und Parasit.,' II. 1887.

SYPHILIS

The primary syphilitic sore or chancre is a localised inflammation in an abrasion—the seat of infection—with subsequent induration, necrosis, and ulceration of the superficial layer or layers. Under the microscope the connective tissue of the cutis or mucosa, as the case may be, is densely infiltrated with round cells; most of these do not differ in size from white blood corpuscles, but some are larger, have two or three nuclei and a considerable amount of protoplasm, and in size of the cell and number of the nuclei correspond to giant cells. The spreading of the induration consists in the infiltration involving larger and larger areas, while at the same time the superficial layers undergo necrosis and disintegrate into a *débris*, whereby an open sore is established. When the chancre heals, the round cells infiltrating the corium are gradually absorbed and disappear, the fibrous connective tissue becomes more abundant, and ultimately by contracting, forms a dense cicatrix. The secondary symptoms are established by acute localised inflammations of the skin, lymphatic glands, and mucous membranes: the tertiary by round cell infiltration, and chronic inflammation in the skin, bones, brain, and viscera. In these inflammations and infiltrations the microscopic appearances do not differ from other non-syphilitic inflammations. Gummata and condylomata, or mucous patches, are localised inflammations, i.e. round-cell infiltrations, and distended and engorged vessels; the epithelium of the surface and the corium or mucous membrane being also the seat of infiltration with round cells; in fact, the disease is similar to what is called in pathology a *granuloma*. The fate of the gummata and condylomata is fatty degeneration, caseation, absorption, and cicatrisation.

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[1] Kalning, *Archiv f. Veterinärwiss.*, I. 1891, St. Petersburg; Preusse, *Berliner thierärztl. Wochenschr.*, No. 29, 1891; Heyne, *Berl. thierärztl. Wochenschr.*, 1891, Nos. 33 and 39; Pearson, *Zeitschr. f. Veterinärk.*, No. 5, 1891.

As to the etiology of syphilis, various microbes have been described. Foremost is the bacillus of Lustgarten,[1] which is by many considered to be the bacillus of syphilis. Lustgarten found in the tissue of primary syphilitic sores certain bacilli, generally in comparatively small numbers: they resemble in size and staining power the tubercle bacilli, are straight or slightly curved, sometimes thicker at the end than in the middle, uniform or granular; they occur chiefly in pairs within the protoplasm of the round cells, but occasionally also between the cells. These bacilli have this peculiarity, that they can be stained by a special method: sections of chancre are placed in gentian violet aniline water, are then decolourised in solution of permanganate of potassium; by this all the elements of the tissue lose the stain except the bacilli. De Giacomi achieved the same result by decolourising the sections (after staining) in solution of ferric chloride. While numerous observers (Doutrelepont and Schütz, Matterstock, E. Fraenkel) have found the bacillus of Lustgarten in the syphilitic foci of the skin and mucous membrane of the mouth, and in the syphilitic gummata of the viscera, others like Alvarez and Tavel, Klemperer, Kübner, Zeissl, Baumgarten, and others have searched for them after the approved methods, but have failed to find them. Besides, Alvarez and Tavel[2] have proved that bacilli identical with Lustgarten's bacilli in size, aspect, and peculiar staining power occur in the normal sebum or smegma of the genital organs, and this has been confirmed by other observers, so that the claims of Lustgarten's bacilli to be considered as the bacilli of syphilis rest at present on insufficient evidence.

There is also no doubt that though many competent observers have searched for them in the syphilitic tissues in congenital syphilis, they have failed to find them. Kassowitz and Hochsinger described in the cutaneous papules in hereditary syphilitic children, streptococci plugging almost completely the small vessels of the corium; Eve and Lingard[3] described, in syphilitic tissues and in the blood, bacilli resembling the tubercle bacilli in size and aspect, and have cultivated them on blood-serum; they do not show any peculiarities in staining.

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[1] *Die Syphilisbacillen*, Wien, 1885.

[2] *Bull. de l'Acad. de Méd.*, August 1885.

[3] *Lancet*, No. 15, 1886.

Finally, Disse and Taguchi[1] describe capsulated diplococci, which they found in syphilitic tissues; they cultivated them, and with such cultures produced by inoculation of rabbits, dogs, and sheep, a chronic disease which they consider analogous to syphilis; but all attempts to produce a definite disorder in any animal by means of inoculations of veritable syphilitic tissue, hitherto attempted by many competent observers, have yielded only negative results.

RHINOSCLEROMA

A peculiar chronic disease, starting in the nasal and pharyngeal mucous membrane and extending to the outer nose (skin) and downwards into the larynx and trachea, prevalent in Austria and in some Eastern countries. It is essentially a firm, nodular swelling, consisting in a circumscribed infiltration with round cells of the mucous membrane and skin; in the former it leads to degeneration of the superficial layers, including the epithelium of the surface, and to ulceration. In the skin the nodular swelling of the corium persists for a long time without leading to ulceration. In a microscopic section the connective tissue is densely infiltrated with round cells; among these there occur peculiar hyaline globules, larger than the round cells. These were first recognised by Mikulicz,[2] and are known as Mikulicz' cells. Mikulicz, Dittrich, Walkanitsch, and others consider that these Mikulicz cells are produced by hyaline degeneration and swelling, with solution of the nucleus, of certain epitheloid cells of the tissue, not the ordinary round cells. In sections through rhinoscleroma, stained with methyl blue, the Mikulicz cells are easily recognised by their deep blue staining; some are many times larger than the ordinary round cells of the tissue, others are much smaller, and of no greater diameter than a leucocyte. Some are only a single, large, homogeneous sphere; others are made up of two or three small homogeneous spheres, but one can distinguish in all of them a thin pellicle of granular investment, including at one place a flattened nucleus; where the cells are made up of two or three smaller spheres, these latter have only a common investment. These Mikulicz cells resemble, therefore, fat cells; but instead of a fat droplet or fat droplets, there is inside them a homogeneous colloid material. We therefore think that the general statement, that these Mikulicz cells are hyaline degenerated cells, is only partially correct, but think rather that some of the cells of the scleroma tissue form at the expense of their protoplasm hyaline globules, in the same manner as certain cells form fat droplets; the nucleated investment would represent the remnant of the original cell protoplasm. A. von Frisch[3] was the first to show that in the tissue of rhinoscleroma, particularly in the Mikulicz cells, there occur small oval bacilli, either single or as dumb-bells. He cultivated them and used them for inoculations on animals, but without result. Cornil and Alvarez[4] then showed that the rhinosclerom bacilli possess a gelatinous capsule, and therefore resemble the pneumonia bacilli of Friedländer (*see* a former chapter). Dittrich has made extended experiments and observations on these rhinosclerom bacilli, and showed that morphologically and culturally they are, distinguishable, but only with difficulty, from Friedländer's bacilli; though he maintains that in some minute details as to staining and as to appearance in gelatine cultures the one can be distinguished from the other. This is, however, not admitted by many observers. Alvarez, Paltauf and Von Eiselsberg, Wolkowitsch, and Dittrich found these bacilli also in the lymphatics of the surrounding tissue. Paltauf and Von Eiselsberg,[1] then Dittrich, Babes, and others, produced in guineapigs, mice, and rabbits a septicæmic infection similar to that producible by Friedländer's bacilli, but no chronic nodular disease.

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[1] *Deutsche med. Woch.*, No. 14, 1886.

[2] V. Langenbeck's *Archiv f. kl. Chir.*, XX., p. 485.

[3] *Wiener med. Wochenschrift*, No. 32, 1882.

[4] *Archives de Physiologie normale et path.*, VI., 1885.

The constant presence, then, of the capsulated rhinosclerom bacilli in the scleromatous tissue, particularly the Mikulicz cells, is a fact of which there can be no doubt, but it is equally a fact that they are identical with the bacilli of Friedländer; their causative relation to the rhinoscleromatous process is, therefore, more than doubtful, or at any rate not sufficiently supported.

CHAPTER XXVI

TUBERCULOSIS

Tubercle is, after Virchow, a granuloma or a round-cell new growth, at first grey and translucent, then undergoing from the centre outwards a necrotic change leading to degeneration or caseation; the part degenerated is yellow. This necrotic or caseous change extending from the centre, while the periphery increases by the deposit of new round-cell elements, wider and wider areas of tissue become involved, and thereby both the grey periphery and the yellow or caseous centre enlarge in diameter. The caseous portion softens by suppuration, so that the tubercle becomes gradually changed into an abscess, the suppuration being sustained by the peripheral portion of the tubercle. Tubercles differ in structure: some, e.g. those of the lung, liver, and lymph glands of man, are in most instances, in the early or grey stage, typical granulomata or round-cell new growths in the connective tissue; then they become reticulated, and, instead of finding dense aggregations of round cells between delicate bundles of fibrous tissue, we find a more or less regular reticulum of cells; in the peripheral part the reticulum is somewhat arranged like a capsule of concentric layers; in the reticulum of the centre we find large irregularly shaped, cylindrical or spherical cells, containing numerous nuclei, generally disposed in an annular zone in or near the periphery of the cell protoplasm; in such reticular tubercles it is the central portion containing the giant cells that first undergoes necrosis and caseation. Some tubercles never assume this reticular condition, but pass directly from the grey stage, or granuloma, into the caseous or yellow tubercle. Then there are tubercles, e.g. some forms of acute miliary tubercles in children, when the lung is found studded with grey tubercles, which do not at all resemble granulomata, being in reality groups of air cells filled with, and distended by fibrinous deposits with leucocytes in the centre. There are sometimes tubercles in which few or no giant cells are found, e.g., tubercles in the brain, leading to suppuration and formation of abscess, tubercles of the spleen and of the liver; while in other cases the tubercles in the same viscera contain abundance of giant cells, chiefly in connection with the reticular form. In bovine tubercle, in tubercle of the fowl, and in artificial tuberculosis in guineapigs, giant cells are abundant in the tubercles, which do not present the reticular form; they are present in tubercles of man in the lung, liver, membranes of the brain, spleen, and marrow of bone. Most tubercles are at first granulomata in the connective tissue; i.e. derived from connective-tissue cells (Virchow), as well as white blood corpuscles (Cohnheim). This is the case with the tubercles occurring in the lymph follicles of the lymph glands, and of the intestine (Peyer's and solitary glands), in the Malpighian corpuscles of the spleen, in the peribronchial lymph follicles, in the connective tissue of the pia mater of the brain, and in the interlobular connective tissue of the liver: other tubercles owe their origin partly to round cells, and partly to a multiplication of epithelial or endothelial cells; such is the case with the tubercles in the alveolar cavities of the lung, in the interlobular bile ducts, in the lymphatic vessels and lymphatic sinuses, in the intima of large blood-vessels (aorta), and in the glands of the mucous membranes and skin. Amongst the cells constituting a tubercle the gradual enlargement of at first small round cells (lymph cells or leucocytes) into larger epithelial-like cells, with one or more large nuclei, can be distinctly inferred from all transitional forms between the two, and therefore the large cells with large nuclei, though resembling in aspect epithelial cells, cannot be declared to be epithelial in origin; but in tubercles formed in connection with epithelial and endothelial tissues (*see* above), epithelial cells do contribute to the formation of the cells constituting the tubercle.

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[1] *Fortschr. d. Med.*, No. 19, 1889.

Then, again, while in some tubercles, necrosis and caseation, though extending to a large extent, do not lead to suppuration—e.g. in the liver and spleen—there are others which, sooner or later, after caseation has set in, commence to soften and suppurate, e.g. the tubercles of the lung in man, in cattle, in artificial tuberculosis of animals, the tubercles of the lymph glands, and the tubercles of bone-marrow in man. All tubercular masses (nodules, patches, and streaks) sooner or later caseate, i.e. the tissue undergoes necrotic change; the cells become opaque and change into granular *débris*, not taking a stain; no nuclei are visible in them: fatty and other coarse granules are, however, numerous; further, calcareous deposits may take place in these caseous masses if they do not become softened and absorbed.

It is impossible to recognise by their structure under the microscope some tubercules as 'tubercles,' if they are only in the condition of granulomata, or if they are suppurating and without any giant cells; but if reticular and with giant cells, the presence of these latter would generally decide the diagnosis. As we shall presently see, however, there is an infallible test for diagnosis, and that is the presence of the tubercle bacilli of Koch. But from microscopic structure alone some tubercles, notably those without giant cells, cannot easily be identified. Of course there are in many cases sufficient indications of a gross anatomical nature, e.g. the disseminated nature in the different lymph glands and viscera, the condition of caseation, &c., which enable us to form a fairly correct diagnosis, but in cases in which only in one or the other organ we find a nodule, caseous or not, the diagnosis is very difficult, in fact in many such instances it cannot be made; then the bacteriological examination alone is decisive. No doubt many pathologists have had not a few times to examine deposits, few in numbers, in the lungs and liver of man and animals (fowls, cats, sheep) which were firm and caseous, some even calcareous, and where the histological examination was insufficient to permit of a correct diagnosis; it is an every-day experience of those whose practice lies more in the direction of diseases of the chest that it is difficult in some cases to make a correct diagnosis from the symptoms and physical appearances of the lung affection; yet the test for the tubercle bacilli at once makes the diagnosis certain. Not long ago a case of multiple brain abscess occurred, and the patient died. There were no tubercles in any of the viscera of the chest or abdomen. The histological examination of the infiltrated tissue forming the wall of the abscess did not show any appearance characteristic of tubercle—no giant cells, no localised granulomata ; the tissue was uniformly infiltrated with round cells, gradually becoming denser towards the interior ; no diagnosis of tubercle could be made from the histological characters, and yet by testing for the tubercle bacilli, and finding them in large numbers in and amongst the round cells, the diagnosis was at once made certain.

The first decisive experimental proof that tuberculosis is a communicable disease has been given by Klencke and Villemin,[1] the latter showing that if guineapigs are inoculated with tubercular matter, such as sputum derived from a tuberculous patient, a chronic disease is produced, which has the distinct characters of disseminated tuberculosis in the lymph glands, the lungs, the serous membranes, the liver, and the spleen. The deposits are at first minute and grey, not larger than a pin's head ; they gradually enlarge and caseate in the centre, the caseation spreading over the whole tubercle. Wilson Fox, Burdon-Sanderson, Klebs, Cohnheim, Chauveau, and others have repeated and confirmed these experiments. Inoculations with bovine tubercular matter were also made on guineapigs and rabbits, and true disseminated tuberculosis produced. The feeding of pigs, guineapigs, and rabbits with tubercular matter, both human and bovine, produced disseminated tuberculosis. The tubercular deposits of all such experimental animals when transferred to normal animals again produced tuberculosis.

When inoculation into the subcutaneous tissue of the groin of guineapigs is carried out with a minute particle of human tubercular material,[2] after a lapse of about fourteen days, more or less, the lymph gland nearest the seat of inoculation can be easily felt as a firm swollen nodule of the size of a pea ; after a lapse of a further ten or twelve days the first gland is much enlarged (size of a bean or filbert) and may already have become changed into an abscess firmly fixed to the skin, whilst one or other lymph gland near it can now be felt as a firm swollen nodule. The abscess soon opens, and discharges thick creamy pus, a persistent sore is established, and though it may from time to time become covered with a scab or crust, the accumulation of thick pus underneath soon causes it to be again opened. The other enlarged lymph glands about the seat of inoculation also become converted into abscesses. On killing the animal after four to six weeks, we find at the seat of inoculation an open sore discharging thick pus, the subcutaneous connective tissue around and for some distance being hyperæmic and œdematous. In connection with the sore we find a chain or a packet of swollen firm lymph glands (from the size of a split pea to that of a bean) containing cheesy, yellow deposits. On cutting into such a gland we find it very juicy, and containing larger or smaller yellowish masses ; in the largest glands some of these masses are found changed into thick creamy pus. At or about this stage, i.e. after four to six weeks, in most instances either no tubercles visible to the unaided eye are as yet found in the lungs, or only very few minute punctiform nodules; in the enlarged spleen we find numbers of minute granules projecting above the surface of the capsule, thus making the surface uneven and rough. In the liver there are numerous minute grey, punctiform nodules, which in some places have a tendency towards confluence ; on section greyish streaks are recognised under a lens between the normal red liver tissue, and the whole organ is slightly enlarged. The omentum also shows numerous minute opaque patches, which are more numerous and larger than those normally found. The lymph glands in the porta hepatis are large and firm, so also those in the hilum of the spleen; the mesenteric glands are large and firm. In the marrow of long bones, grey and even caseous tubercles can be distinguished. If the animal is allowed to live, it will be found gradually getting thinner towards the third or fourth month, and it does not generally die before the end of the third or later than the end of the fifth month, the average duration being 100 to 120 days after inoculation. On *post-mortem* there is found a large discharging sore at the seat of inoculation, from which extends a chain or packet of lymph glands from about the size of a bean to a large filbert; on cutting into such a gland numerous yellow irregular cheesy deposits are seen, some softened and purulent. The lymph glands behind the sternum, at the root of the lung, of the porta hepatis, at the hilum of the spleen, of the mesentery, of the pelvic cavity, and of other localities are swollen, firm, and contain larger or smaller irregular patches of caseous deposit. The lungs are enlarged, and sometimes crowded with, at other times containing a limited number of, tubercular deposits of all sizes—from that of a millet seed to that of a pea—and in all stages; some grey with the beginning in the centre of yellow caseous change, others entirely yellow and caseous, most of them firm, the largest softened in the centre and representing the first trace of cavernæ; where crowded they become confluent. The spleen is greatly enlarged, of from four and five times to ten times its original size, riddled with caseous tubercles, in many places confluent into irregular yellow firm patches. The liver is permeated with greyish white to yellow nodules, streaks, and patches, the larger ones of a greenish yellow colour and firm. The omentum is one mass of confluent tubercular nodules and patches. The diaphragm contains whitish-grey streaks and patches of tubercle. So also the pleura. Rarely is there tubercle in the kidney.

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[1] *Etude sur la Tuberculose.* Paris, 1868.

[2] Any material derived from tubercle, no matter whether grey, caseous or purulent : caseous or purulent lymph gland, sputum or purulent matter of the caseous tubercles of the lung, tubercle of the spleen or liver, may serve the purpose.

Rabbits, inoculated subcutaneously in the inguinal region with human tubercular sputum, show very much less pronounced disseminated tuberculosis than guineapigs; after twelve to sixteen or more weeks the animals are found much emaciated; the lymph glands of the inguinal region are enlarged and caseous; in the lungs are few or no tubercles, in the liver a few tubercles, some grey, others yellow; the spleen is enlarged, and contains many tubercular deposits; the mesenteric and other abdominal lymph glands are swollen, firm, and caseous; and the process, on the whole, is very distinctly less intensive and extensive than in the guineapig. The writer has seen numerous cases in which, after twelve to sixteen weeks, the only organ containing numerous tubercles was the spleen, the liver contained only few, the lungs none.

The feeding of guineapigs and rabbits on human tubercular matter produces tuberculosis, but with this difference, that while in the guineapig it leads to general disseminated tubercular deposits, this is far less so in the rabbit. In the guineapig, if the animal is killed after six to eight weeks, we find distinct tubercular deposits in the wall of the small intestine, the tubercles being situated in the Peyer's glands of the ileum and the ileo-cæcal valve; they are of various sizes, and more or less caseous in the centre; the mesenteric glands are always enlarged, and contain firm caseous deposits. The liver also shows grey tubercular nodules and streaks; the spleen is slightly enlarged and granular. The whole process, judging from the amount and progress of the changes, starts in the lymphatic follicles of the ileum, and spreads thence into the mesenteric lymph glands, liver, and spleen. The lungs as yet show no tubercles. If the disease is allowed to run its course, the animal becomes greatly emaciated, and dies in about four or five months or earlier; we then find tubercles in all the lymph glands, in the viscera, in the marrow of bone, and in serous membranes; but the changes in the abdominal viscera are the most extensive, those of the thorax considerably less.

In the rabbit, on the other hand, feeding with human tubercular matter produces considerably less result; in a large percentage of cases, even after many weeks, caseous tubercles are found only in the lower ileum and mesenteric glands. The spleen, liver, and lungs appear free, and only in a few cases are these organs involved, and then but to a small degree, viz. containing only few tubercles.[1]

In the fowl, tuberculosis can be produced both by subcutaneous inoculation and by feeding with human sputum, although all animals are not equally susceptible. In most cases tubercles of the spleen, in others of the spleen and liver, are the result; the intensity of the process in both these organs is striking only in a few very successful cases, and in these we find both those organs enlarged and containing numerous spherical, firm, white nodules, from the size of a millet seed to that of a pea. When superficial they project over the capsule. In many other cases tubercles are found only in the spleen. The remarkable fact is that in most instances, notwithstanding the tuberculosis going on in their spleen, the animals are very fat; when, however, the liver becomes involved to a large extent, the animal is found emaciated.

In guineapigs, rabbits, and fowls, in all tubercular deposits giant cells are numerously met with. Tuberculosis can be produced in animals (guineapigs, rabbits) by intraperitoneal injection, and by inhalation. By a spray-producer, finely divided tubercular matter can be distributed in the air in which guineapigs sojourn; the majority of these will become affected with general tuberculosis after the usual lapse of time, the lungs being here most advanced in the tubercular process. The writer has had guineapigs kept in their cages in the ventilating shaft at Brompton Hospital, and thereby general tuberculosis was produced in the great majority of these animals: caseous tubercles in the lungs, in the lymph glands, spleen, liver, and pelvic glands, was the result; proving that the air of any place in which tuberculous persons sojourn contains the tubercle virus, and must therefore be considered as not free from danger.

BOVINE TUBERCULOSIS

Tuberculosis is a common disease of the bovine species: the number of tubercular animals is astonishingly great. In many instances, on slaughtering them, only the lungs are found diseased, presenting a peculiar and characteristic appearance, viz. the surface of the lung, pleura, and diaphragm presenting numerous flat oval, spherical or irregular shaped nodules, some with short broad basis, others with long thin basis or stalk fixed on to the organ. Sometimes clusters of them project from the general surface; these appearances have caused the disease to be called 'the grapes,' in German 'Perlsucht.' Not only the surface of the lung, but also the interior contains numerous such nodular deposits. They differ considerably in size, some being not larger than a split pea, others as large as a filbert or walnut, or larger. Some of these nodules are filled with thick, creamy pus, others are yellow and caseous but firm, and others again contain calcareous matter. Under the microscope the nodules contain in the periphery, round cells in a fibrous matrix, and amongst them very numerous giant cells of different sizes, from that of only twice or thrice the size of an ordinary leucocyte to that of a real giant cell with twenty to thirty and more nuclei all regularly disposed near a peripheral zone of the cell. Near the caseous portion these huge giant cells are very conspicuous; the caseous part may still show the outline of the giant cells, but their nuclei do not take the stain, and the whole tissue of the caseous portion is a granular *débris*. In early cases of bovine tubercle the development of the tubercles in and from the lymphatic vessels of the pleura can be readily followed. This has been correctly described by Sibley. In pronounced and advanced cases, freely projecting nodules, as also nodules within the substance, having a great tendency to suppurate, are met with in the lymphatic glands, in the spleen, liver, and even in the milk glands. In these latter, the condition assumes an important practical aspect, since the udder of a cow may contain tubercular nodules without these being easily diagnosed, and may give to the milk infective properties. Although in light cases the milk gland is found free from tubercles, yet in many advanced cases purulent tubercular deposits have been demonstrated in the udder.

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[1] Eisenhardt (*Centralbl. f. Bact. und Parasit.*, X., No. 18) found in 1,000 *post-mortem* examinations of human tubercular bodies, children under sixteen excluded, only one solitary instance of primary tuberculosis of the intestines.

In the lymph glands, spleen, and liver, the character of the nodules is the same as in the lung, and giant cells form a very conspicuous feature.

Tubercular nodules of large size (about the size of a bean or filbert), caseous in the centre, are occasionally found in the spleen of young calves; this would suggest that the process is inherited, for it can hardly be assumed that in an animal six to eight weeks old tubercles already caseous had been acquired after birth: in fact, if careful search is made for these tubercles in young calves derived from tubercular cows that have no tubercles in the udder, it will be found that they are not at all of such rare occurrence as is sometimes assumed. On the other hand, calves fed on milk derived from tubercular cows, in whose udder tubercles can be demonstrated (by the tubercle bacilli test), develop tuberculosis of the intestine, the mesenteric glands, spleen, and liver; but for the development of these many weeks and months are required. While, then, calves acquire tuberculosis by feeding on milk tainted with the tubercular virus, some undoubtedly inherit tuberculosis directly from their tubercular mother.[1]

Infection with general tuberculosis of guineapigs and rabbits by bovine tubercular matter, by feeding, or by subcutaneous or intraperitoneal inoculation, is easily achieved; the result is more intensive and much more rapid than by infection with human tubercular matter. Guineapigs, subcutaneously inoculated, develop disseminated tuberculosis of the lymph glands, lungs, liver, spleen, serous membranes, and marrow of bone in less than half the time; in some cases the animals die in about five to six weeks with remarkably widespread and advanced tubercular deposits. Also as regards rabbits, the process is much more rapid and more intensive; for while these animals, as mentioned above, after inoculation with human tubercular matter, develop, as a rule, only a more or less mild form of tuberculosis, limited chiefly to some lymph glands, spleen, and perhaps the liver, after inoculation with bovine tubercular matter they show very numerous tubercular deposits in the lungs, liver, spleen, all lymph glands, and even in the kidneys. The same results are obtained by feeding rabbits and guineapigs with bovine tubercular matter. Here also the process starts with tubercles of the ileum, then spreads to the mesenteric glands, the pelvic glands, the omentum, spleen, and liver, and finally the lungs and sternal and bronchial lymph glands. The difference in the intensity and duration of the process is decidedly more pronounced with bovine than human tubercular matter, and also in the rabbit the difference between feeding with bovine and with human tubercular matter is striking; so that there can be no question that bovine tubercular matter acts in a conspicuous degree more virulently than human tubercular matter, both in guineapigs and rabbits.

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[1] In the Second Congress on Tuberculosis in Paris (*Semaine Médicale*, 1891), Vignal, Bernheim, Hutinel, from experiments and observations made on guineapigs and rabbits, conclude that transmission of tuberculosis from the mother to the offspring is of very rare occurrence.

The feeding of calves with milk derived from an udder containing tubercular deposits produces tuberculosis in these calves; but milk coming from a healthy udder (though the cow has tubercles in the lung) fails to produce tubercle.

Hirschberger ('Experim. Beiträge zur Inf. der Milch tuberculöser Thiere,' München, 1889) finds that at least five per cent. of milch cows are tubercular, and though in many cases their milk is not different from the milk of normal cows, and no tubercle bacilli can be detected, yet the same milk injected into the peritoneal cavity of guineapigs produces miliary tuberculosis in the peritoneum, spleen, and liver. Out of twenty series of experiments only once could the tubercle bacilli be demonstrated in the milk, and yet in ten such experiments in which the milk did not show tubercle bacilli, it nevertheless produced tuberculosis on intraperitoneal injection. Hirschberger explains these results by assuming that though tubercle bacilli were not present in the milk as bacilli, their spores must have been present. Bollinger ('Münchner med. Zeitschr.,' No. 43, 1889) shows that milk from the healthy udder of tubercular cows loses its infectivity after dilution (1 : 40, 1 : 50, or 1 : 100). Therefore, he warns against the consumption of milk coming from one particular cow, but encourages the mixing of milk from many cows, since thereby the tubercular milk would become greatly diluted by normal milk, and thereby lose its infective power; a conclusion that must be admitted as quite possible from the observations just stated, though it is contrary to what one would *à priori* have expected, viz. one would have thought it better not to mix, in order to avoid possible contamination of normal milk.

Tuberculosis in Fowls

Koch first pointed out (International Medical Congress, Berlin, 1890) that the tubercular process naturally occurring in fowls is different from human or bovine tubercle, the tubercle bacilli of the fowl behaving differently in culture and in the animal experiment from those derived from human or bovine tubercle. A. Maffucci ('Zeitschr. für Hygiene und Infect.,' Band XI., 3, p. 445) has minutely studied and described these differences.

The important question that is constantly being asked is this: Can bovine tubercular matter produce tuberculosis in man? No direct evidence of this has as yet been given, but there are a number of ascertained facts which make it extremely probable that bovine tubercle is so communicable. On the one hand, the pathology of bovine and human tubercle makes it quite acceptable that the two are variations of one disease. Although in some minute details they differ from one another, e.g. in the bovine species, tubercle of the lung assumes the form of the so-called grapes, which it does not in man, they nevertheless must both be regarded as the disease tuberculosis (and as we shall presently see, both are caused by the same kind of bacillus), i.e. a granuloma in the lymph glands, viscera, and marrow of bone, leading to caseation and associated with the same kind of microbe; it is also true that in the guineapig and rabbit the result of inoculation and feeding with the two viruses is not quite identical, but they have, nevertheless, this in common, that by subcutaneous inoculation and feeding, typical tubercle can be produced. These differences may be and probably are entirely due to the fact that the tissues of the bovine species are not identical with those of man, and that the activity of the virus is different according as this is bred on bovine or human soil, that is to say, that the degree of virulence of the two is not the same. As we shall see below, there is other evidence to show that bovine tubercle is of greater virulence than human tubercle.

On the other hand, the numerous cases of acute miliary tuberculosis in children, not derived from tubercular parents, become otherwise very difficult of explanation. It will not be contested that tuberculosis differs from some other infectious diseases in this: that direct communicability from person to person, though proved, is yet of rare occurrence. Villemin himself described cases where a husband communicated tuberculosis to his wife, and *vice versâ*; other cases are on record where a phthisical person (a midwife) infected new-born children with tuberculosis; but on the whole, taking into account the comparatively extremely rare occurrence of tuberculosis in persons who, coming from a healthy stock, have been in communication with a tubercular patient, it is quite justifiable to assert that direct infection of the healthy from the tuberculous is a rare event.

So that on this assumption the comparatively numerous cases of miliary tuberculosis in children are difficult of explanation, and we are perhaps not far wrong in attributing such cases to the consumption of cows' milk containing the tubercular virus derived from a tubercular udder. Likewise, Dr. Sims Woodhead states that the numerous cases of tabes mesenterica (tuberculosis of the intestines and mesenteric glands) of children are attributable to the consumption by these children of milk derived from the tubercular udder of the cow. But it must not be forgotten that tuberculosis of the human species is in the majority of cases directly inherited, though the disease as a rule lies latent till the person attains the teens or twenties.

A good many pathologists still maintain with Virchow that heredity means only a greater predisposition, a weakness of the lung and other tissues, and that if tuberculosis actually makes its appearance in such a person, say when in the teens or twenties, it probably is due to infection with tubercle. Now, this view dates, as Baumgarten[1] very correctly points out, from a time when tuberculosis was not yet known to be an infectious disease; at the present time it has no clear meaning, because in no other infectious disease is anything so vague admitted. Heredity of disease always means, and can only mean, the transmission of the disease germ directly from the parent to the offspring. In inherited tuberculosis the disease germs lie dormant during the period of the active growth of the tissues, to start multiplying when this has become less active. The cases of latent tuberculosis are not quite so rare as has been represented, since on the *post-mortem* table one has not so very unfrequently the opportunity of finding a calcareous or caseous nodule that is really a solitary tubercle in a lymph gland, in the lung, in the liver, or in the spleen.

Direct infection by inoculation is known to occur on the hands of butchers, cooks, and others handling carcases of tubercular cows, and also amongst those who make *post-mortems* on human tubercular corpses (tuberculosis cutanea verrucosa); but in all these instances inoculation is followed by local tubercle, which after suppuration leaves no further mischief behind.

A further point in connection with bovine tubercle is the question whether in a tubercular cow the whole carcase should be declared dangerous for consumption, or, after the removal of the tubercular organs, should the consumption of flesh be considered as of no danger ? If, in a tubercular cow, the tubercular viscera or any part thereof be considered dangerous for human consumption, then the whole animal must be considered dangerous. Tuberculosis being disseminated and involving in the cow such very different and distant organs as the lungs, the lymph glands, the abdominal viscera, and the marrow of bones (MacCall), it must be clear that the tubercular virus, though it has not its habitat in the blood, is nevertheless being disseminated by the blood to the different organs, or is carried from one part to a distant one by means of the blood-vessels. True, Klebs, Cohnheim, Sanderson, and the writer himself, have shown that in artificial tuberculosis in guineapigs infected by way of the peritoneum, the process spreads by means of the lymphatics from the peritoneum through the lymphatics of the diaphragm to the organs of the thorax; also that after subcutaneous infection the virus spreads along the lymphatic vessels and lymphatic glands, but on the other hand, tubercular deposits in the intima of the carotid artery, the aorta, and other large arteries have also been recorded. Besides, the early appearance of tubercles in the red marrow of the bones in guineapigs (Klein and Lingard), after subcutaneous inoculation, and in the bone marrow of the cow in general tuberculosis (MacCall), conclusively show that the tubercular virus becomes disseminated through the general blood circulation. By injection of tubercular virus (artificial cultivations of tubercle bacilli) into the veins of the ear in rabbits, the writer has, like Koch, produced most marked miliary tuberculosis in the lungs and liver: both organs were riddled with vast numbers of minute grey tubercles (fig. 141). After three weeks this condition was established, and in the lung the formation of the tubercles in connection with blocking of capillary blood-vessels could be clearly demonstrated. Such being the facts, we are justified in saying that the dissemination of the tubercular virus by the vascular system is proved, and under this aspect all organs may, at any time, harbour in their blood-vessels the tubercular virus, though this may be only on transit to a distant place, and though a particular organ (e.g. muscle) does not contain any discernible tubercular deposits.

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[1] *Lehrbuch d. pathol. Mycologie*, p. 626.

Kastner ('Experim. Beiträge zur Inf. des Fleisches perlsüchtiger Rinder,' München, 1889), it is true, has failed to produce tuberculosis in guineapigs into whose peritoneal cavity the juice of the muscular tissue of bovine animals affected with tuberculosis was injected, but such negative results do not justify us in denying the possibility of infectiveness of the flesh at one time or another. Besides, more recently Steinheil ('Münchener med. Woch.' 1889, Nos. 40 and 41) has shown that injection of muscle, in which no tubercle could be detected, but taken from persons dead of phthisis, into guineapigs produced well-marked tubercles in fifteen out of eighteen animals so inoculated.[1]

Cohnheim and Salomonson[2] were the first to show that in all tubercular material a specific virus is present. On injecting a small particle of such matter into the anterior chamber of the eye, they noticed that after the first result due to the injury has passed off, the introduced particle gradually undergoes diminution to almost complete disappearance, but in about a fortnight or three weeks a crop of minute grey nodules which in reality are typical young tubercles are found in the iris; these gradually enlarge, and like all ordinary tubercles undergo caseation. The tubercular process is at first localised to the iris, but it gradually spreads to the cervical lymph glands, and ultimately leads to general tuberculosis of the other lymph glands and viscera exactly as after subcutaneous inoculation. This typical production of a crop of grey tubercles on the iris by tubercular matter enabled Cohnheim and Salomonson to differentiate tubercular from non-tubercular matter, and they have formulated from this the axiom that only matter derived from tubercle is capable of producing tubercle, and that whenever any substance is found capable of producing this iris tuberculosis, it is derived from tubercle. By this clear proof for the first time a means was offered of making an easy differential diagnosis between tubercular and non-tubercular matter, a diagnosis which those who, at former times, were engaged in work on tubercle found extremely difficult. As is well known from clinical observation, the diagnosis of tuberculosis of the lungs is sometimes associated with difficulties: the physical examination and symptomatology do not always insure a correct diagnosis. It is true that Villemin had proved by experiment that tuberculosis is inoculable, and Wilson Fox had insisted on the specificity of tuberculosis by numerous experiments which he himself had carried out, yet there were authorities who did not draw this sharp distinction, but were rather inclined to the view that artificial tuberculosis is due to matter derived from a variety of sources not necessarily always tubercular, having undergone some process of intensification, and become infective. For that period, therefore, the exact proof given by Cohnheim and Salomonson marked a very important step, though the exact nature of this specific tubercular virus remained undetermined. The next discovery was that of Koch,[1] who showed what this nature is; he demonstrated a particular species of bacilli, now familiar to all pathologists as the *tubercle bacillus*, which he found only in tubercle and in no other disease, a bacillus so peculiar and so constant that its important diagnostic value was at once recognised. No matter whether it is a nodule in any tissue or organ that does or does not present the typical pathological (gross and minute) characters of the classical tubercle; no matter whether in man or the bovine species, in the sheep, in the monkey, dog, cat, rat, mouse, rabbit, guineapig, fowl, or ostrich, if in such a nodule the bacilli characteristic of tubercle can be demonstrated, *that nodule is tubercle, and the disease is tuberculosis.* The discovery by Koch of this fundamental fact marks one of the most brilliant and most practical discoveries of modern medical science; the diagnosis of tubercle, once so difficult to make with certainty, is now, by means of the demonstration of the presence of the tubercle bacilli, one of the easiest and at the same time one of the most important helps in the formation of a correct diagnosis in some otherwise doubtful cases. Koch further proved that not only are these particular bacilli present in all and every tubercle of man and brutes, but he also showed that these bacilli can be artificially cultivated outside the animal body, and with such cultures typical and general tuberculosis can be produced by inoculation, the tubercles thus produced again containing the same tubercle bacilli; in short, *he conclusively established that these bacilli are the* vera causa *of the disease tuberculosis.* The whole problem concerning one of the most widespread, fatal, and at that time little understood diseases of man and animals was by these researches at once cleared up, and considering the difficulties in the solution of the problem and the necessity of having had to invent special methods by which this research was carried to a successful issue, we have no hesitation in saying that this discovery of Koch marks one of the most important, if not the most important, epoch in pathology. Many are the workers who since Koch have contributed towards further details as to this matter; but without any intention of minimising the importance of any and every contribution of fact towards a clear understanding of this disease and its prevention, we are, we think, within the limits of absolute correctness in saying that Koch's publications on tuberculosis ('Berliner klin. Woch.,' 1882; and 'Mitth. aus d. k. Gesundheitsamte,' II.) contain almost the complete solution of the problem. Koch showed that by staining tubercular materials (in cover-glass specimens or in sections) with aniline dyes (methyl blue) to which a little alkali is added, and then subjecting them to decolourising agencies (nitric acid, hydrochloric acid), all the colour is lost from the elements of the tissue with the exception of the tubercle bacilli themselves. Ehrlich then showed that by staining tubercular material in fuchsin aniline oil and then treating the specimen with one-third nitric acid (ordinary nitric acid one part, water two parts), all the colour is removed except from the tubercle bacilli, these retaining the red colour; by after-staining with vesuvin or methyl blue the tissue is again stained brown or blue respectively, while the tubercle bacilli retain the beautiful bright red colour. The leprosy bacilli, the syphilis bacilli, and the smegma bacilli have the same power of withstanding the action of nitric acid after fuchsin staining, but other bacteria become decolourised. The best method, and one always used with success, is to stain with Ziehl's carbol fuchsin from twenty to thirty minutes at 35° to 40° C., then washing in water for a second or two, then for a few seconds (five to ten) in $33\frac{1}{3}$ per cent. nitric acid, washing again in water and placing in methyl blue aniline oil for five to ten minutes, washing and treating in the usual way, according to whether a cover-glass specimen or section is being dealt with. The writer has never seen failure with this method: the tubercle bacilli are always brought out with striking clearness.

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[1] See also the discussion on this subject by Bang, Arloing, Nocard and others at the International Congress on Hygiene, London, 1891.

[2] *Uebertragbarkeit d. Tuberculose*, Berlin, 1877.

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[1] *Berliner klin. Wochenschr.*, 1882.

A great many modifications for staining the tubercle bacilli have been published, all good to a lesser or greater degree, but the one just mentioned is as good as any and in many instances has proved simpler and better. The tubercle bacilli always occur in tubercular nodules, sometimes more numerously where caseation has already set in than in the earlier stages. They occur isolated or in groups between the cells constituting the tubercle, or they are found singly or in small groups within the larger cells; when present in giant cells they are found in large numbers, forming a sort of annular zone around the central portion. In some giant cells their number is at times very limited, and Koch has concluded from this fact that the tubercle bacilli suffer death in the giant cells, and hence disappear from them. In human tubercle, the tubercle bacilli are, as a rule, between the elements constituting the tubercle; but, as just mentioned, they also occur within the uni- and multi-nucleated cells. In bovine tubercle, however, the rule is that they are mostly present in the uni- and multi-nuclear cells, and only when these degenerate and break up do they become free; in the caseous matter they are present in groups in the granular *débris*. In tubercle of rabbit (lung and liver), produced by inoculation with bovine tubercular matter, or with artificial culture derived from bovine tubercle, the presence of tubercle bacilli within the cells—small, large, and giant cells—is very conspicuous, and yields very remarkable specimens (*see* fig. 110).

The tubercle bacilli in human tubercle are delicate cylindrical rods measuring 1·5–4 μ; many are straight, with rounded ends, but others are slightly curved; in preparations (sputum, purulent matter, or sections) stained in the above manner the bacilli always appear composed of granules, that is to say, within a faintly stained sheath the protoplasm is segregated into deeply stained, cubical, spherical, or rod-shaped granules; between the granules the sheath is empty, but these empty places are not to be taken for bright spores, as is done by some observers, nor is it proved that the above granules are spores. That the tubercle bacilli contain spores is proved by numerous experiments of drying and heating, to be detailed below; but what the character of these spores is, and how they appear in the bacilli, has not been satisfactorily shown. In bovine tubercular matter prepared in the same manner the tubercle bacilli are, as a rule, shorter and thinner, and though we do not for a moment question the fact that some tubercle bacilli of human tubercle are as short and thin as those of bovine tubercle, we are confident from numerous observations that the majority of the human tubercle bacilli are longer and thicker than those of bovine tubercle; besides, in preparations stained in the above manner, the segregation of the protoplasm within the sheath, though also present in many tubercle bacilli of bovine tubercle, is not so general and uniform as in those of human tubercle. But these minute differences need mean nothing more than differences due to the different soils on which the bacilli were reared. Such morphological differences in size and aspect in one and the same species of microbes are well known to occur in other instances if the microbe be cultivated in different soils. When the tubercle bacilli from any source (bovine, human, or from artificially infected animals) are passed through the rabbit or the guineapig, in these animals the new crop of bacilli all appear to be morphologically the same.

The tubercle bacilli show definite characters in cultivation. Koch succeeded in cultivating them on solid blood serum. On inoculating the slanting surface of the solid serum with tubercular matter, and provided no other bacteria are introduced, Koch noticed the first signs of growth in ten to fourteen days. Koch used for inoculations of serum tubes the tubercular deposits of a swollen lymphatic gland of a guineapig, three to four weeks previously inoculated with tubercular matter, clean sterile instruments being used. After ten to fourteen days the first signs of the growth of the tubercle bacilli showed themselves in the form of whitish points and patches, resembling dry scales. On further growth they enlarged, and where close together they coalesced into dry whitish scaly masses with irregular outline. From such primary cultures, sub-cultures on serum were then carried out. But under a magnifying lens, or better under the microscope, the growth and multiplication of the tubercle bacilli can be seen before the end of the first week. Peculiar curved, or convoluted, or S-shaped whitish lines, which prove to be strands of tubercle bacilli, are noticed even at this early stage. On agar broth the growth is very limited, and also in broth. But Roux and Nocard showed that by adding 6 per cent. of glycerine to agar meat infusion, or to meat broth, the tubercle bacilli can be brought into rapid and extensive multiplication. On glycerine-agar-beef infusion the tubercle bacilli grow very rapidly, the growth being visible after six to eight days, and after several weeks to several months covers the whole surface as a whitish, peculiarly wrinkled, dry film, extending as a white thin pellicle over the condensation water at the bottom of the tube. In order to obtain good and copious growth it is necessary to keep the tubes capped from the outset. The writer has obtained very copious growths in alkaline broth, to which a piece of boiled white of egg was added. In such tubes the broth kept at 37° C. remains clear for four or five days, then minute flocculi and granules appear at the bottom and along the wall of the tube, where it is in contact with the broth; after a fortnight the growth becomes abundant, and on shaking the broth is made turbid by the numerous flocculi. On potato moistened with broth it is likewise possible to obtain growth. Temperatures of 36° to 38° C. are most favourable for the growth ; below 30° or above 42° C. no growth can be noticed.

Koch has shown that by subcutaneous or intravascular injection, by inhalation, and by inoculation into the peritoneum or the anterior chamber of the eye, &c., of artificial sub-cultures removed by many generations from the original source, typical tuberculosis is produced in all animals susceptible to tubercle (guineapigs, rabbits, dogs, rats, mice), and that the tubercular deposits in these experimental animals again contain abundantly the tubercle bacilli ; thus, the final and exact proof that the tubercle bacilli are the *vera causa* of the tubercular process was definitely established. The intravascular and intraperitoneal injection produced the most striking and rapid results.

Although the growth on glycerine agar mixture is copious, it yet has this drawback, that by continued sub-culture the virulence of the bacilli is diminished. The first sub-cultures act virulently, inasmuch as they produce general and fatal tuberculosis on inoculation into guineapigs ; thus even with a fourth and fifth sub-culture the writer has succeeded in producing the same results as by directly using sputum or bovine tubercle, but after the eighth or tenth generation it has not been possible to produce general tuberculosis and death of the guineapigs by inoculation. The writer has found that if from an agar-glycerine culture, which, owing to age or sub-cultures, has completely lost its virulence, new cultures are established in alkaline beef broth, to which a piece of boiled white of egg is added, these sometimes again acquire a somewhat virulent character.

By injection of large quantities of cultures (a full Pravaz syringe of a milky salt mixture) directly into the ear vein of the rabbit the writer has produced in two weeks extensive tuberculosis in the lung, both lungs being riddled with minute tubercles, the small ones (varying in size from about the point to the head of a pin) being grey, the larger ones yellow and caseous in the centre (*see* also Koch). In guineapigs inoculated with considerable quantities of late sub-cultures on glycerine agar, firm-swelling and purulent change in the nearest lymph gland can be produced, leading to abscess and ulceration ; in such glands the presence of crowds of tubercle bacilli can be easily demonstrated in cover-glass specimens ; but the glands gradually diminish in size, the ulcer heals, and after eight to ten weeks little can be noticed ; the animals do not grow thin and do not die.

Eight such guineapigs were after six months re-inoculated with virulent tubercle (tubercle of bovine lung) ; they all developed in the normal time general tuberculosis, and died. On the *post-mortem* being made no difference could be detected between them and control animals. But it is justifiable to suppose that with the proper degree of virulence, i.e. the proper stage of attenuation, the cultures might produce a more severe effect than the above cultures, an effect which, though not leading to the development of general tuberculosis, might yet protect the animals against a second inoculation of virulent material.

As a rule, cultures made in alkaline beef broth to which a piece of boiled egg albumen has been added behave in the same manner as glycerine agar sub-cultures ; that is to say, in the former the virulence of the tubercle bacilli becomes gradually attenuated by sub-cultures, so much so that injecting a considerable quantity of a late broth sub-culture into rabbits (the ear vein), or, better still, into the muscle of the abdominal wall, only a local abscess is slowly developed ; the pus and particularly the wall of the abscess contain the tubercle bacilli. After the abscess is opened, spontaneously or by incision, the wound heals and the animal completely recovers. With Dr. Schorstein the writer has made experiments with the pus of such a local abscess, and it was found that on subcutaneous inoculation into guineapigs a much more marked result is produced; in fact, general tuberculosis ensues, thus proving that the tubercle bacilli, attenuated in the broth culture, when passed through the guineapig regain their virulence. A condition similar in principle to this will be mentioned of the tubercular virus of human scrofula (*see* below), this being an attenuated form of the tubercular virus, but gaining in virulence as it is passed through the guineapig.

The sub-cultures on glycerine agar show after several months besides the typical forms of cylindrical and granular tubercle bacilli also some filaments made up of rods and granules. Some of these filaments are remarkable by their being undoubtedly branched like the mycelium of a hyphomycetes, and, further, by some being club-shaped at the end or beaded in their course; these club-shaped and branched filaments are the more numerous the older the culture. Although the club-shaped and beaded condition might correspond to involution of the threads, the branched condition cannot, and therefore the club-shaped forms may well represent the growing ends of the threads of a mycelium; the two together, i.e. club-shaped and branched threads, would, therefore, indicate that the typical tubercle bacillus is a phase only in the development of an organism, which under certain conditions (glycerine agar) declares its true nature and origin, being, namely, comparable to a fungus having a mycelial stage (*see* Klein in the Report of the Medical Officer of the Local Government Board, 1889, Plate XXVII., figs. 61, 62, 63).

Scrofula and Lupus

Koch and many other observers have shown that, both in scrofula and lupus, tubercle bacilli occur, and that with both these materials general tuberculosis can be induced in guineapigs. But since these two diseases are in the human subject well-marked disorders, distinct from pulmonary tuberculosis, it is necessary to assume that the tubercle bacilli in the three diseases possess some functional differences. To say that lupus is a form of tuberculosis of the skin does not cover the facts, since real tuberculosis of the skin does occur, and is totally different from lupus; so also scrofula is not merely tuberculosis localised in the cervical lymph glands, since, in many instances, it does not lead to pulmonary and general tuberculosis, whereas the true tuberculosis of lymph glands does so. It is quite feasible to assume that both lupus and scrofula are tuberculosis, but that in origin and virulence their tubercle bacilli are different from the bacilli causing true tuberculosis. That the virulence of the virus of lupus and scrofula cannot be the same as that of the material of human and bovine pulmonary tubercle is proved by experiments of Dr. A. Lingard,[1] who showed that the duration and extent of the disease induced by inoculation of lupus or scrofula into guineapigs is quite different from that induced by pulmonary tubercular matter, and, further, that if a guineapig is made tubercular with scrofulous matter, and the tubercle of such an animal is again transmitted by inoculation through several generations of fresh guineapigs, the disease thus produced gains gradually in shortness of duration and intensity, until after several generations the same effect of general tuberculosis is produced as that produced directly by matter of pulmonary human tuberculosis.

That the tubercle bacilli in one phase or another do contain spores has been shown by Koch, who found that tubercular sputum when thoroughly dried maintains its virulent character. The writer has repeated these experiments, and can say that tubercular matter (from human tubercles of the lung and lymph glands, from bovine tubercle of the lung, tubercular matter from lymph glands, lung, liver, and spleen of guineapigs dead of general tuberculosis artificially produced) bears thorough drying without losing its virulence. The writer has also repeated these experiments with regard to artificial cultivations: a small particle of culture is mixed well in sterile water; of this mixture a thin film is spread out on a glass slide and this is thoroughly dried, then the film is again scraped off, mixed with a drop of water, and with this mixture guineapigs are subcutaneously inoculated: these become affected with general tubercle in the usual way.

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[1] Report of the Medical Officer of the Local Government Board, 1888, p. 462.

Now, if the tubercle bacilli had no spores, they would not in all cases survive thorough drying; no sporeless bacillus is known that can survive thorough drying; whereas all bacilli in the stage of spore-bearing survive this process. Further, tubercular matter and cultures of tubercle bacilli survive temperatures up to 100° C. Non-spore-bearing bacilli and micrococci are killed by being exposed for five minutes to a temperature of 65–70° C., whereas spores of other bacilli withstand much higher temperatures. Tubercular sputum distributed in salt solution does not lose in the least its virulence by being kept at 100° C. for one to two minutes. Nor does a solution of perchloride of mercury kill the tubercle bacilli in the way it does sporeless bacilli. Dr. Lingard found (Report of Medical Officer of Local Government Board for 1885, p. 183) that solution of perchloride of mercury, one grain of mercuric bichloride to 960 grains of water, that is to say, about one in 1,000, although it kills the bacilli in human tubercular matter when acting on it for four hours, does not do so in the case of bovine tubercular matter, since not even eight hours' exposure to the solution is sufficient to destroy the infective power of that material. This also shows, as has been mentioned already on a former page, that bovine tubercular matter is of a higher degree of virulence than human tubercular matter.

The important observations of Schottelius ('Centralbl. f. Bact. und Parasit.,' VII., 9), that tubercle bacilli taken from the lung of phthisical persons, buried for years, still possessed on inoculation into rabbits and guineapigs the capability of producing artificial tuberculosis, have been already mentioned.

Schottelius further shows that the tubercular lung kept in soil (enclosed in a wooden box) shows an incomparably large increase in temperature, amounting in some experiments to a rise to 34° C. This would indicate that under these conditions the tubercle bacilli in such a lung are capable of continuing to live and multiply. From these experiments the conclusion must be drawn that the tubercle bacilli are not true parasites, but belong to the ectogenic microbes, which can live and thrive independent of a living host.

In August 1890, on the occasion of the International Medical Congress held in Berlin, and in subsequent publications, Koch announced that by experiment he had ascertained that when guineapigs, previously made tubercular by subcutaneous inoculation, are inoculated, at a date when the animals show the signs of tuberculosis, with extract (glycerine extract) of dead tubercle cultures, the growth itself from the surface of serum or glycerine agar being rubbed down and extracted with glycerine, the tubercular glands of these animals undergo a rapid necrosis and elimination, brought about by an acute reactive inflammation beginning in the tissues around the tubercle, but the tubercle bacilli themselves are not affected by it. He then applied this method of injecting glycerine extract of dead tubercle cultures—tuberculin—in very small doses, 0·001–0·01 gramme, into the human subject: lupus, bone tuberculosis, and early pulmonary tuberculosis. The result was remarkable, since most patients affected with one or another form of tuberculosis reacted very conspicuously to such injection: high temperature, great local congestion and inflammation in lupus, and bone tubercle. Persons not affected with tubercle do not, as a rule, show any reaction to such small doses. In lupus, and bone and joint tubercle, the tubercular tissue becomes necrotic, is either spontaneously eliminated, as in lupus, by the reactive inflammation of the surrounding tissue, or can be removed by surgical aid, as in tuberculosis of bone. Tuberculin is, then, a distinct means of diagnosing tubercle in the living subject, otherwise not easily diagnosed. Also with regard to bovine tubercle, the injection of tuberculin has proved of great value, since early tuberculosis, not otherwise apparent, can be diagnosed by the definite reaction (rise of temperature) that occurs in such animals, but not in animals free from tubercle. These observations have been recorded by a number of accurate experimenters on the Continent, in England, and in America.

Weyl has analysed the tuberculin, and found that the essential portion of it is a substance related to mucin, not to albumin. Dr. W. Hunter ('Brit. Med. Jour.,' 1891) has more accurately determined the various principles present in tuberculin.

Good therapeutic results have been obtained with the tuberculin in lupus, bone tuberculosis, and in early pulmonary tuberculosis; in advanced pulmonary tuberculosis the injection of tuberculin has in some cases produced a dissemination of the tubercle bacilli and acute miliary tuberculosis in the lung and other viscera (Virchow). The same or similar results have been obtained in tuberculised guineapigs by Baumgarten after injection of tuberculin.

CHAPTER XXVII

LEPROSY—ACTINOMYCOSIS—TRACHOMA

LEPROSY

LEPROSY belongs to the group of granulomata, inasmuch as in the majority of cases—the tubercular form—the connective tissue of the skin, and to a smaller extent of the mucous membrane of the mouth, pharynx, larynx, cornea, testes, parenchymatous organs, and marrow of bone, are the seat of nodular deposits made up of cells. These cells are spherical, oblong, spindle-shaped, or irregular; in the central part of the nodules or tubercles they are more closely placed side by side; in the peripheral, i.e. towards the surrounding portions, they are less crowded; few of the cells are small like leucocytes; the majority are twice or thrice or more times this size. But whether small or large they generally possess a single nucleus; the large cells have received from Virchow the name of *leprosy cells.* Where the cells are closely aggregated there is very little other tissue between them. In the peripheral parts, however, there are connective tissue bundles between them. The tubercle or nodule enlarges by masses of cells becoming deposited in the surrounding tissue—fibrous tissue, muscular tissue, cartilage, &c. The nodules may also enlarge towards the surface, i.e. involve the epidermis or epithelium; and this latter then ultimately sooner or later becomes destroyed, and a discharging, ulcerating sore is established; but this is not the necessary fate of the tubercles, since some, having reached their maximum growth, dwindle down and become absorbed, leaving an œdematous, puffy, discoloured patch of the skin behind. In all the nodules, however, numerous cells are constantly disintegrating, the nucleus swells up and disappears, and then the cell substance disintegrates. In the second form, the anæsthetic form, there are no nodules formed, but the nerves undergo a fibrous degeneration; in the early stages the connective tissues of the nerve—the general epineurium and the perineurium—contain in their lymph channels and lymph spaces cells which also gradually invade the connective tissue within the nerve bundles, i.e. the endoneurium; gradually the connective tissue thickens, and in the nerve bundles the nerve fibres undergo degeneration leading to the disappearance of the axis cylinders and medullary sheath and the transformation of the whole nerve fibre into a connective-tissue bundle.

That leprosy is a communicable disease is proved in several instances: Europeans living with lepers (Father Damien), sexual connection of Europeans with lepers (in India and other Eastern countries); but by what ways the leprosy virus enters the body is unknown. Likewise it is not known why the disease is, on the whole, so rarely communicated to healthy persons repeatedly in contact with lepers, for the fact that the disease is one of the least easily communicated is a conspicuous feature in all countries where leprosy prevails. Occasional cases of leprosy occur in England and in America nowadays, some of which have contracted the malady in the East: they present sometimes a very severe form, but no communication to other persons has been known to occur. The writer has seen a very severe case of leprosy in a young man, who contracted the disease in India: the patient's face and ears were really one large sore discharging purulent matter very copiously; every trace of this discharge was crowded with round cells and large leprosy cells, all of them crowded with the leprosy virus, i.e. the lepra bacilli, numerous cells in a state of disintegration, and hereby the bacilli becoming free and scattered in the fluid part. Fig. 147 is a representation of this discharge, and yet, though the patient voided many thousands of the bacilli in every drop of the discharge, no case of leprosy was known to have been communicated by it. But though the disease seems to be communicated with difficulty, it behoves us in the face of the copious crop of lepra bacilli yielded by the leprous ulcers to be on our guard and to keep lepers as much isolated as possible; and this wise precaution is, as is well known, practised in Norway, as also in many places in the East and West, where leprosy prevails.

A microscopic section through a leprous tubercle (figs. 145 and 146) shows the tubercle to be a granuloma, i.e. an aggregation of cells, each and all of them literally filled with minute bacilli. A. Hansen ('Virchow's Archiv,' Band LXXIX. and XC.) was the first to have observed this fact, and he justly regarded these bacilli as the virus, i.e., as the bacillus lepræ. Neisser ('Breslauer ärztl. Zeitschrift,' XX. and XXI., 1877; 'Virchow's Archiv,' LXXXIV.) then showed that these bacilli have peculiar characters of staining, and he also claims to have succeeded in artificially cultivating them. Cover-glass specimens are made from a scraping or part of a leprous nodule, or the discharge of a leprous ulcer, by spreading it out in a thin film on a cover-glass, drying and heating, then staining after Ehrlich's method of staining for tubercle bacilli (in carbol fuchsin for twenty to thirty minutes at 35° C., then washing in water, then for a few seconds in $33\frac{1}{3}$ per cent. nitric acid, washing in water, drying, and mounting); such specimens show the leprosy cells, some small, some very large, all crowded with minute stiff, thin, and relatively long bacilli. Many cells are in a state of disintegration, or broken down into granular *débris*, and in accordance with this, numerous bacilli are found free, isolated or in groups. The large and middle-sized cells are particularly interesting, since their substance is almost entirely occupied with the bacilli arranged in bundles, which bundles often lie towards one another at sharp angles, and hereby produce a very striking effect. Sections through a leprous nodule stained in the above manner (carbol fuchsin, $33\frac{1}{2}$ per cent. nitric acid, washed in water, then counter-stained in methyl-blue aniline water for fifteen to thirty minutes) shows the nuclei of the tissue blue, the cells forming the leprous nodule red, owing to the fact that their substance is crowded with the (red) leprosy bacilli ; in such sections nothing can be seen of the nuclei or substance of the leprosy cells, the cells being marked merely as groups of densely aggregated leprosy bacilli (fig. 146). While, then, the lepra bacilli have characters in staining by which they resemble the tubercle bacilli, they differ according to Baumgarten and others in this, that they stain in alkaline methylene blue with conspicuously greater difficulty than the tubercle bacilli. The lepra bacilli are on the average 4–8 μ long, and about 0·8 μ thick ; in well-stained and well-washed specimens they, like the tubercle bacilli, show segregation of the protoplasm (deeply stained granules) in a faintly stained sheath ; the bacilli appear straight or slightly bent and more or less possessed of pointed ends. The remarkable constancy with which the lepra bacilli occur in dense crowds in the leprosy cells, and their peculiar characters, are striking. Neisser maintains that he has succeeded in cultivating the lepra bacilli, but the evidence adduced is not deemed sufficient. Bordoni-Uffreduzzi ('Zeitschrift f. Hygiene,' III., p. 178) maintains, however, that he has produced artificial cultures from the leprosy nodules of bone marrow, on glycerine serum to which peptone and salt had been added, kept at 35–37° C. The line of inoculation became marked as a yellowish irregularly outlined band ; the serum was not liquefied. On glycerine agar, inoculated with considerable quantity of leprous material, the same kind of growth took place. In glycerine agar plates the colonies that grew on the surface and in the depth, seen under a magnifying power of 100–200, were rounded reticulated patches, with dark thick centre.

Inoculation experiments on animals, though repeatedly tried by a large number of observers—Damsch, Vossius, Melcher, Ortmann, Wesener, Thin, and others—by the introduction of large bits of leprous nodules into the subcutaneous tissues, the peritoneum, and the anterior chamber of the eye in various animals, have yielded only negative results, so that the conclusion is justified that leprosy is not transmissible to the lower animals.

Dr. Arning inoculated in November 1885 a Hawaiian man named Keanu with leprosy, and the disease (typical tubercular leprosy) subsequently developed. But Dr. Sidney Bourne Swift, resident physician, leper settlement, Molokai, Hawaiian Isles, states, in an article to the 'Occidental Medical Times,' April 1890, that this man Keanu is one of a family of lepers (Keanu's son, sister's son, and wife's brother are, or were, lepers), and that the disease as it appeared in Keanu was too rapid to have been the result of the inoculation by Dr. Arning ('Brit. Med. Journal,' I., 1890, p. 917).

ACTINOMYCOSIS

Bollinger[1] was the first who showed that various tumours in cattle, leading to chronic suppuration, e.g. in the jaw, tongue, pharynx and skin, are one and the same disease, due to a parasite which he constantly found present in those tumours in the shape of yellow granules. These granules, when examined under the microscope, appear to be made up of radially arranged fibres and clubs, which Professor Harz designated *actinomyces*, or *ray fungus* ; and the disease it causes is therefore called *actinomycosis*. Israel[2] next observed a disease in the human lung, in which he found a mycelial fungus that was afterwards identified by Ponfick as the ray fungus seen by Bollinger in the tumours of cattle. Ponfick himself published several cases of actinomycosis in man.[1] Since these observations, the reports of a large number of cases, in cattle, pigs, and man, have been published, in which tumours, abscesses, and suppurations, &c., were found in one or the other of the following organs : the jaw, skin, tongue, pharnyx, larnyx, lung, intestine, liver, and brain, and proved to be due to the same parasite—actinomyces.

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[1] *Centralbl. f. d. med. Wiss.*, 1877, No. 27.

[2] *Virchow's Archiv*, Band LXXIV., 1878.

Pathology.—As regards the pathology of the nodules produced by the ray fungus, these belong to the granulomata, i.e. they are in the first place aggregations of round cells in the connective tissue ; around the fungus which forms the centre of the new growth the cells constituting the infiltration are ordinary lymphoid cells, some are several times larger than the rest, and possess several nuclei ; these latter, viz. the multi-nucleated cells, are generally found in the immediate neighbourhood of the fungus ; many of the round cells contain coarse granules, which gradually change into fat globules. As the central fungus mass enlarges by active growth, so the nodule enlarges by the infiltration with round cells spreading into the surrounding tissues. In a later stage the central portion softens and becomes purulent ; an abscess is thus formed which, opening on to the surface, or into the nearest cavity, soon discharges copious pus ; when the abscess opens on to the free surface, e.g. jaw, skin, pharynx, larnyx, lung, or intestine, an ulcer is established, which enlarges as the infiltration in the periphery proceeds. In the discharge of the abscess a number of yellowish minute granules can be found ; these granules looked at under the microscope are a mass of the ray fungus.

It has now been established that carious teeth in some cases represent the point of entrance for the fungus ; in these cases the alveolar process of the jaw becomes the place for the growth of the fungus, leading to the formation of a hard tumour, gradually becoming converted into an abscess and ulcer ; the infection, i.e. invasion of the fungus, then spreads to the lymph glands and skin nearest to the affected jaw, and there produces a tumour, then suppuration and an ulcer. Or it invades the tonsils and the pharnyx, either primarily or after it has once taken root in the jaw, tongue, or cheek. Or it appears primarily in the larynx, trachea, and lung ; and in these cases the fungus has evidently been introduced by the air during inspiration ; in the case of the lung, extensive interstitial inflammation is set up, leading to abscesses perforating into a bronchus. Or it primarily invades the alimentary canal and leads to abscess and copious suppuration there, and even to perforation of the part ; in the case of the alimentary canal evidently the fungus has entered with the food. From the alimentary canal the disease spreads to the mesenteric glands and the liver ; and in this latter organ it produces abscess, which may open through the peritoneum into the peritoneal cavity, or, if previously an adhesion with the abdominal wall has been established, may perforate outwards. In all these instances the discharged pus contains the yellow granules, i.e. groups of the ray fungus. In the case of the skin the fate of the tumours is suppuration and formation of abscess, and this opening on the surface leads to the formation of a sore. The primary infection of the skin by actinomyces has been proved (E. Müller, 'Mitth. aus d. chirurg. Klinik,' Tübingen, Band III., 3) in a case in which a wood splinter in the skin had evidently been the means of providing an entrance for the fungus. Both in man and cattle these various ways of infection with actinomyces have been observed in many cases.

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[1] *Bresl. ärztl. Zeitschrift*, I., p. 117. *Berl. klin. Woch.*, 1879. 'Die Actinomykose.' Berlin, 1881.

Now the important question that presents itself is this, Where does the fungus generally live? The various ways above mentioned in which it invades the organism, at once suggest that it has its usual habitat in the outside world, i.e. that it is an organism which is introduced into the animal body from without, and is not directly derived from an infected animal or man. It is a prevalent opinion that the natural habitat of the ray fungus is on cerealia, that it lives on these parasitically, and through and from these enters the animal body through wounds, abrasions, &c. Johne ('Centralbl. f. d. med. Wiss.,' 1881, No. 15) has shown that actinomyces occurs normally in the pits and the loculi in the tonsils of the pig; in these instances there were always present bits of ears of barley covered with what appeared to be ray fungus. Jensen ('Deutsche Zeitschrift f. Thiermed.') observed an epidemic of actinomycosis in cattle fed on barley; and Piana described actinomyces nodules in the tongue of cattle, where in the midst of some of the nodules there were present portions of vascular fibre-tissue of corn surrounded by ray fungus. Finally, Soltmann ('Breslauer ärztl. Zeitschrift,' 1885, No. 3) made the remarkable observation of an actinomyces abscess in the region of the dorsal vertebral column, caused by the perforation (during swallowing) of an ear of barley; the abscess opened and the ear was discharged. Fischer ('Centralbl. für Chirurgie,' No. 22, 1890) describes a similar case: a labourer on chewing barley pierced into his tongue a portion of the awn. Eight days after, a swelling appeared on the punctured spot, and a fortnight later a tumour of the size of a filbert could be distinctly felt. After eighteen days an incision was made into the tumour, and the examination of the scanty pus and the tissue of the tumour revealed the presence of numerous yellow granules—actinomyces. A fragment of the awn was also removed from the interior of the tumour, and on examining it under the microscope was found covered with clumps of actinomyces. So that from all this the conclusion appears justified that actinomyces is a fungus having its habitat on certain cerealia, and with and by them is introduced into cattle and man.

As mentioned above, the tumours and abscesses occurring in one or the other organ contain peculiar minute granules and clumps, visible to the unaided eye, generally of a yellowish, but occasionally of a greenish-yellow tint. Under the microscope they appear made up of a central mass of fine granules, or of a distinct trellis-work of fine branched threads; next is a zone of coarser granules, which look not unlike cocci; but when this or the central zone is teased out, it can be shown that the granules are not really granules, but in reality are densely aggregated and twisted branched fine fibres, the 'granules' being only due to optical sections of the fibres; at the periphery of the mass are glistening, densely and radially aggregated, flask-shaped or club-shaped bodies called the 'clubs' (fig. 117). The central mass is occasionally found in a state of calcification: this is not seldom the case in cattle.

That these clubs are an important and characteristic feature in the morphology of the fungus is shown by the name of ray fungus and by the fact that, as is commonly observed—at any rate in cattle it is common—all the actinomycosis nodules and abscesses contain one or more central masses of these radiating aggregations of clubs. But also in the human disease the clubs are with few exceptions present, though there are cases described in which the fungus was said to have been represented only by a dense felt-work of branched fine threads. The first question that offers itself for answer is, What is the significance of these different morphological features, and what is the life history of the fungus?

In sections through the affected tongue of cattle we find numerous round-cell granulomata between the muscular bundles and in the mucosa, some quite superficial and penetrating from the papillæ into the surface epithelium; in all of these there are one or more groups of the ray fungus; in suitably stained sections (rubin, 2 per cent. watery solution for several hours, then washed in water and stained in methyl-blue aniline water for fifteen to thirty minutes) the ray fungus group appears as an irregularly spherical mass or more commonly, particularly when large, as a lobed mass, composed of a central faintly stained homogeneous, or only faintly granular mass; around this is a zone deeply stained in blue, and owing to its being composed of densely aggregated and twisted branched threads, it looks not unlike cocci. The peripheral part is made up of conical, or cylindrical, or club-shaped corpuscles of different lengths and thicknesses, deeply stained pink, closely placed side by side, and all radiating by longer or shorter thin, pink, filamentous stalks from the next, the blue or 'granular' zone; each of the 'clubs' possesses a faintly stained homogeneous sheath. In human actinomycosis, and also in actinomycosis of cattle, the central mass is sometimes recognisable as a dense felt-work of fine branched threads; from the periphery of the mass longer threads project, each or only some of them possessing a terminal enlargement; in other cases the terminal club-shaped enlargement is the only distinct portion.

Now, some observers consider the clubs as indicating an involution or a degeneration-phase of the threads, and, further, the above granules of the second zone as indicating a coccus phase of the threads, and for this reason consider the ray fungus as belonging to the species of cladothrix, a polymorphous fungus, in which the threads may break up into, or develop from cocci and shorter or longer rods or bacilli. Now, we are opposed to this view, for we constantly find in actinomycosis of cattle some of the smaller, i.e. younger tumours, contain fine clubs in isolated examples or in small groups, without any filamentous or granular centre; in the preparations stained successfully as above we find appearances which place us in full agreement with Crookshank ('Transactions of the Med. Chir. Soc.,' 1889): single clubs very conspicuous by their deep red staining attached to a short single or branched stalk, free or enclosed within a nucleated cell. Further, we can find, free or enclosed within a larger mass of protoplasm, a small homogeneous mass from which are budding out two, three, or four clubs of different lengths and with very short stalks; these structures being stained bright pink stand out very conspicuously from the blue ground.

Further, we find spherical or oval globules recognisable by their deep pink staining becoming constricted off from the free end of the clubs. Putting these features together, there can be no difficulty in recognising a striking likeness between the ray fungus and a mycelial fungus: the fine branched threads being the mycelium, and the clubs being the growing ends of the hyphæ, such as are common to some hyphomycetes; these clubs, with their power of sprouting and giving off conidia (the above spherical or oval globules), would render the appearances easily intelligible. Further, the central part is the only part which in any way can be said to represent the portion which is actually degenerating, since it often contains calcareous deposits. This view of considering the clubs as the sprouting parts and conidia-bearing ends, and the threads as analogous to the mycelium of an oïdium-like fungus (Bollinger, Israel and Bujwid), is the one which stands better in harmony, we think, with the actual facts than the view that it belongs to a species of cladothrix (Boström, Paltauf, Afannassiew[1]). Israel has shown that the ray fungus can be artificially cultivated, but Boström was the first who succeeded in artificially producing good cultures of this fungus. On blood serum, and on agar at 33–37° C., the fungus forms whitish granules, which rapidly enlarge; they show a yellow or reddish, round, knobbed centre, from which start fluffy nebulous branched masses; after five to six days the growth has reached its height. The presence under the microscope of the branched mycelial threads and of the clubs was established in these cultures. Paltauf and Afannassiew have confirmed these observations. As a rule, however, the granules in the cultures are made up entirely of dense felt-works of branched threads (*see* fig. 118).

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[1] Sauvagean and Radais (*Annales de l'Institut Pasteur*, vi., 4, p. 242, April 1892) consider actinomyces as a mycelial fungus, Oospora bovis.

On glycerine agar the actinomyces forms a film composed of distinct yellowish-brown round granules; in broth it also forms distinct granules, varying in size from that of a millet seed to that of a small pea; on gelatine good growth can be obtained at 20° C., in the form of a whitish-yellow pellicle made up of granules; the gelatine is liquefied, but remains quite clear.

An important fact, established by Israel, Boström, Rotter and others, is this, that the ray fungus of man can by inoculation produce typical actinomycosis in cattle, and there is therefore the greatest probablity that the converse also holds good.

The chronic necrotic disease occurring in India, and known as the madura disease, or the fungus disease, has been shown by Kanthack to be due to, and caused by, a fungus resembling in most respects actinomyces. This was found to be the case in the yellow or pale variety, as also in the black or melanoid kind (Pathological Society of London, January 19, 1892).

TRACHOMA

Another form of chronic round-cell growth, i.e. granuloma, is the trachoma conjunctivæ (also called Egyptian ophthalmia): it is a chronic diffuse infiltration of the conjunctiva with round cells, and at the same time a hyperplastic enlargement of the normal lymph follicles of the conjunctiva. The surface of the conjunctiva, besides being abnormally injected, has instead of its smooth, a finely granular character. This chronic process, the trachoma, does not lead to suppuration, but the infiltration and the swelling of the lymph follicles subside, and after fatty degeneration and absorption of the round or lymph cells, a shrinking and cicatrisation of the conjunctivæ take place. Sattler maintains that he discovered in the secretion of the conjunctiva, and in the swollen lymph follicles, a coccus which he cultivated in gelatine, and which he compared to the gonorrhœa coccus. (This last microbe, as has been stated on a former page, does not grow on gelatine.) He also maintains that he produced typical trachoma by inoculation of his cultures into the conjunctiva. The description of what Sattler calls trachoma, produced by inoculation of his trachoma coccus, cannot be accepted as showing that it is genuine trachoma.

Michel described (‘Archiv f. Augenheilkunde,’ XVI., 1886), and grew in artificial cultures, this trachoma coccus, and maintains that he succeeded by inoculation in producing a swelling of the lymph follicles.

As has been mentioned on a former page, Koch, and also Kartulis, have definitely settled that what is called Egyptian ophthalmia is one of three things: (*a*) an acute blennorrhœa identical with gonorrhœa and caused by the gonococcus; (*b*) an acute purulent ophthalmia caused by a minute bacillus to a certain extent similar in morphological and cultural characters to the bacillus of Koch's mouse septicæmia; or (*c*) the chronic granular ophthalmia known as trachoma. Kartulis has shown that either of the first two diseases becoming chronic leads to trachoma, and since the specific organisms causing the first two diseases only exist in the conjunctiva during the acute stages, it follows that the result of the disease, i.e. the granular chronic stage, the trachoma, is not directly caused by, or associated with, any organism of its own. This view of Kartulis seems to commend itself more than that of Sattler and Michel. Kartulis failed to obtain any organisms from the tissue of the swollen lymph follicles in trachoma. And we ought to add that Koch also failed to find bacteria of any kind in the lymph follicles in trachoma.

CHAPTER XXVIII

DISEASES DUE TO FLAGELLATE PROTOZOA

In the chapter on malarial fever mention was made of the presence of crescentic or spherical flagellate bodies, Laveran's corpuscles, which, however, occur only in fever of irregular type. Many species of similar flagellate infusoria are known to inhabit the bodies of invertebrate and vertebrate animals; of these the group known as Monadinæ are in so far of interest that some of them have been found in vertebrates in connection with disease. The genus Trichomonas[1] has been found by Pfeiffer in the oral and pharyngeal mucus of pigeons affected with the chronic necrotic thickening of the mucous membrane, called also 'diphtheria,'[2] the genus which this observer considers to be connected with the cause of the disease. But Löffler (*see* the chapter on Diphtheria) has shown that the disease in the pigeon is due to a specific bacillus, and in this he is fully confirmed by Babes.[3] Pfeiffer in the monograph just quoted still maintains his original assertion, that the disease is due to trichomonas invading and ultimately destroying the epithelial cells. Pfeiffer, however, differs, as regards the life history of this protozoön, from all other observers and writers on protozoa (Leuckart, Bütschli, Dallinger and Drysdale), inasmuch as he describes the formation of spores within the substance of the trichomonas.[4] It ought also to be mentioned that a seemingly identical trichomonas is frequently found in the pharyngeal mucus of perfectly normal pigeons. The writer has had the opportunity of examining a case of this so-called diphtheria in the pigeon, and he found the presence of the parasite in the pharyngeal mucus, but comparing with it a perfectly healthy pigeon, the same trichomonas was also found abundantly in the pharyngeal mucus. Davaine[5] mentions the genus Circomonas, much smaller than Trichomonas, a minute club-shaped, ciliated protozoön, possessed of no envelope, having a pointed prolongation at one end, and a long fine flagellum at the other (Circomonas intestinalis hominis), as occurring in the stools of cases of acute Asiatic cholera; and once he also found them in the stools of a patient in typhoid fever. Lambl as long ago as 1859 described them as occurring in the stools of children in diarrhœa, and Lösch found them also in the stools in cases of dysentery. The writer has had the opportunity of finding in a dead mouse the peritoneal cavity and almost the whole of the intestine distended by, and filled with, a grumous milky fluid, in which, besides leucocytes and micrococci, there were present trichomonas and innumerable circomonas; in fact, the main part of the corpuscular elements was made up of circomonas, many of them moving very rapidly.

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[1] Leuckart, *Die Parasiten des Menschen*, 2nd edition, p. 311.

[2] L. Pfeiffer, *Die Protozoen als Krankheitserreger*, 1890 (Jena), p. 85.

[3] *Zeitschr. f. Hygiene*, Band X.

[4] *Loc. cit.*, p. 85, fig. 26.

[5] *Traité des Entozoaires*, p. xxiii.

A species of flagellate monadinæ was first described by T. Lewis[1] in 1878 as occurring in the blood of normal horses, dogs, and rats; by Evans in 1880 as occurring in the blood of horses in Madrid; by Wittich and R. Koch in 1881 as occurring in the blood of normal badgers. These protozoa are known as the Herpetomonas Lewisii: the body is cylindrical, and often spiral, the flagellum extends as a delicate membrane all along the body of the creature, anteriorly the body terminates as a pointed rigid process. A hæmatozoön which, according to Lewis and Crookshank,[2] is identical with that occurring in the healthy rat was discovered by Evans, but first assumed to be a spirillum, and considered by this observer as the cause of the surra disease, a deadly malady affecting in India horses, mules, and camels in an epidemic form. T. Lewis and afterwards Crookshank[3] gave good photographs of them: the former believes them to belong to the genus Trichomonas.

CHAPTER XXIX

DISEASES ASSOCIATED WITH COCCIDIA

The class of protozoa known as sporozoa—unicellular parasites of fixed form of body, surrounded by a capsule, forming within their body a number of spores, each surrounded by a cuticle, the spores becoming free after the bursting of the capsule, and giving rise to a new parasite—comprises a group which is important to the pathologist, viz. oval coccidia or psorospermia. These are capsulated, uninuclear, oval, protoplasmic corpuscles, in the interior of which a number of spores are developed out of the protoplasm; many of these coccidia are endo-epithelial parasites, and as such are the causes of a chronic hypertrophy of the epithelium. The coccidium best studied is the Coccidium oviforme, causing in the liver of the rabbit a chronic disease of the epithelium of the bile ducts, by which the bile ducts become greatly distended, their epithelium much hypertrophied, and their coats thickened; in consequence of this, whitish-grey nodules, composed entirely of the hypertrophied folded and fringed wall of the bile ducts, appear in the liver.

The columnar epithelial cells lining those hypertrophied bile ducts which harbour the coccidia are, in fact, the soil at the expense of which the coccidia grow and ripen; these latter in their turn, and for their own purpose, causing a continuous multiplication of the epithelial cells. Coccidium oviforme occurs also in the epithelial cells lining the mucous membrane of the intestine in the rabbit. The coccidia are oval corpuscles about 33–37 μ in length, and 15–20 μ broad; each possesses a distinct capsule or cuticle, which at one (thinner) pole contains a minute opening or micropyle. The body of the parasite is a granular protoplasm, in its fully formed state completely filling the space within the capsule, and containing a clear oval nucleus. In this condition they are numerously found in the epithelium, and also free in the cavity of the intestine and the hypertrophied bile ducts respectively; but the majority of forms seen in the epithelium are almost spherical, less oval than the above, and possessing a thinner capsule; in some the capsule is hardly recognisable, they contain a more coarsely granular protoplasm, and within it a clear, spherical nucleus. These are found in great numbers in the epithelium, replacing at points almost completely the epithelial cells, some being distinctly seen within the body of the epithelial cells.

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[1] *Physiological and Pathological Researches*, collected papers of T. R. Lewis, 1888, pp. 604 and 630, Plate XLIII.

[2] *Journal of the Royal Microsc. Society*, November 10, 1886.

[3] *Loc. cit.*

It is not at all easy to decide what is the exact relationship between these smaller, granular, indistinctly capsulated, spherical bodies and the larger, granular, oval, distinctly capsulated coccidia. According to Leuckart,[1] the former would represent young coccidia just germinated from the spores; but this can hardly be correct, considering that in all nodules, particularly the large ones, the small spherical, indistinctly capsulated coccidia abound, and, further, considering that spores are not formed in the coccidia within the animal body. It is therefore more probable that the small spherical coccidia are derived by division from the large oval forms, and in their turn, on their ripening, grow into these latter.

It can be shown that the coccidia first appear in the epithelium of the intestine, and thence find their way into the epithelium of the hepatic duct, and gradually into the bile ducts within the liver. Here their multiplication produces saccular, tubular, and cystic enlargements of the interlobular bile ducts, the wall of which becomes thickened by connective tissue, and folded in many ways. In this manner there are formed in the liver numerous whitish irregularly shaped, firm nodules and cysts, which, when cut into, show a cavity with the thick white wall folded inwards. Under the microscope the folds are made up of vascular connective tissue and covered on the internal or free surface with columnar epithelium, amongst the cells of which numerous coccidia in various stages of development are seen, some of them well buried amongst the epithelial cells, others adhering to the free surface, and others again free in the cavity of the cysts and nodules. As the disease progresses, and larger sections of the liver tissue constantly become involved, necrosis and degeneration by pressure of many liver lobules take place, leading ultimately to the death of the animal. When the coccidia pass out of the animal they undergo changes which lead to the division into two of the plasmatic contents within the capsule; then, again, of each of these into two, so that now each coccidium capsule includes four spherical granular corpuscles, each containing a spherical nucleus; then these corpuscles become oval and surrounded with a thin membrane (*see* Plate XLI., fig. 97), thus representing now the spores or psorospermia. When these find access, again, through water or food to the alimentary canal of the animal, the capsule probably becoming dissolved in the stomach, the spores are set free, and then commence germinating into granular, spherical, nucleated corpuscles, which, while enlarging, surround themselves with a cuticle or capsule with micropyle, and thus form the typical oval coccidium. The researches of Virchow, Kauffmann, Waldenburg, Lieberkühn, Stieda, and last, but not least, of Leuckart, have thrown a good deal of light on the life history of these parasites. Leuckart in his work 'Die Parasiten des Menschen,' 2nd edition, I., 1, gives an exhaustive account of them. The figure 97, *a–g*, reproduced on Plate XLI. is copied from that work. In the human subject nodules of the liver have been observed which were also caused by coccidia, probably Coccidium oviforme. Gubler, Leuckart,

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[1] *Die Parasiten des Menschen*, 2nd edition, I., 1, p. 264.

Dressler and Perls[1] have observed such cases. Amongst other animals, the Coccidium oviforme has been found in the intestines of the dog, cat, sheep, and guineapig. Leuckart states that the intestinal coccidium of the mouse and of poultry belongs to a different species. The writer has seen coccidia in the vessels of the medulla of the kidney both of the guineapig and of the mouse.

Miescher's Coccidia Tubes.—It is not at all rare to find in the muscles of the mouse, wild as well as tame, white streaks visible to the unaided eye as fine white lines between the muscle bundles of the pectoral muscles and of those of the anterior as well as posterior abdominal wall. On examining these lines under the microscope with a low power it is seen that they are composed of tubular granular opaque masses, placed either within the muscular fibres or, as is more common, in the interstices between the muscle fibres. These tubes vary greatly in length, some being several millimetres long, and when between muscular fibres often form continuous chains for considerable distances: the shorter tubes measure 0·7–1 mm. in length. The thickness of the tubes is a little more than twice that of the muscular fibres. They all are tapering towards their extremities. With a high power, a capsule surrounding the dark contents of the tubes can be distinguished. These contents are composed of pale corpuscles, crescentic, kidney-shaped, or, more correctly speaking, looking like thick commas, rounded and slightly attenuated at the ends; in some of them a vacuole can be seen at each end. These crescentic corpuscles measure about 0·01 mm., and are considered to be the spores. Although at first sight they appear densely packed within the tubes, on careful examination they are seen to be grouped into spherical masses, each surrounded by a thin capsule. On teasing out a part of the fresh muscular tissue, many of the tubes become broken, and innumerable isolated crescentic spores are hereby obtained. No movement is possessed by the tubes or the individual spores. That the presence of numerous tubes in the thoracic muscles must be a serious condition with respect to the respiratory action of the chest can hardly be doubted (Dammann, Leisering, v. Niederhausen, and others). The writer has several times had the opportunity of dissecting mice that had died spontaneously, and in which no disease of the viscera could be discovered; but the thoracic muscles and the muscles of the abdominal walls contained the white lines (Miescher's tubes) in enormous numbers. Leuckart does not feel satisfied that these parasites are real psorospermia. Fowls sometimes contain the same tubes, but they have not yet been discovered in the human subject.

L. Pfeiffer ('Die Protozoen als Krankheitserreger,' Jena, 1890) describes the presence of coccidia in the epithelium in variola, vaccinia, varicella, herpes zoster, and other vesicular eruptions. From his description and the illustrations given by him (figs. 28–34, pp. 88–97) he has no doubt that they occur in the substance of the epithelial cells; that here they (the coccidia) multiply by division, and form the spores in their interior. It can be easily shown that certain peculiar bodies do occur in the epithelial cells in these affections, which bodies are not the typical ordinary nuclei, but they can be brought out by various dyes, and thereby can be differentiated both from the cell-protoplasm as also from the ordinary cell nucleus. In sections through the vesicles of sheep-pox, as also of human small-pox, stained first with rubin and then with methyl blue, many of the epithelial cells in the region of the vesicle contain each an oval or spherical homogeneous body, which by its pink colour is well marked off both from the cell protoplasm and the swollen and hydropic cell nucleus, both these being stained blue; but it is extremely difficult—and it seems premature and improbable—to identify them as of the nature of extraneous parasites, viz. coccidia: on the contrary, these bodies look extremely like derivatives of the cell nucleus (*see* below).

It is different, however, in the chronic disease known as epithelioma contagiosum of fowls. This consists in the formation of firm tumours in the mucous membrane of the throat, and also in the skin. Sections through the tumour show the papillæ much enlarged and vascular; they and the corium are infiltrated with round cells, and the epithelium is much hypertrophied.

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[1] See Leuckart, *loc. cit.*, p. 281.

Pfeiffer[1] describes the presence of oval coccidia in the epithelial cells of the tumour. The writer has had occasion to examine sections through the tumours of the skin of a fowl affected with this disease, and he can fully confirm Pfeiffer as to the presence of the oval parasites in the epithelial cells, in some parts every epithelial cell containing, and almost being replaced by, a parasite, the latter being easily brought out by staining the sections first in fuchsin and then in methyl blue.

CANCER

Assertions similar to these, i.e. as to the presence of coccidia, and which are of the utmost importance in etiological and clinical respects, have been also made with regard to cancer, viz. that this disease is due to the presence and growth of coccidia in the epithelium; just as in the above-named nodules in the liver of the rabbit and in the epithelioma contagiosum, the invasion of the epithelium or connective tissue cells—according to the nature of the cancer—by coccidia causes a hypertrophy of the tissue, causes, in fact, the tumour, i.e. epithelial carcinoma or sarcoma. This hypertrophy serves the purpose of supplying the parasite with the host necessary for its growth and multiplication. If this view be correct, cancer would have to be placed amongst the infectious or communicable diseases. That cancer is probably of this nature is indicated already to a certain extent by the following well-established facts :—(1) Heredity. That cancer is hereditary needs no further comment, and like other hereditary diseases is probably of the nature of infectious disorders. The theory that if a disease is inherited this is due to the transmission from parent to the offspring of the materies morbi, is the most ready explanation. (2) The well-known fact that cancer is transmitted in the affected individual from a primary focus to different organs, thus forming metastatic foci. (3) The positive experiments, made within recent years, of successful grafting of cancerous particles from a primary focus to distant parts of the skin of the same individual, by which in the latter new cancerous tissue became developed.

But against these facts must be placed the uniform negative results of producing by inoculation or grafting with fresh cancer material anything like cancer in animals otherwise subject to cancer (dogs). (*See* the carefully conducted numerous experiments by Ballance, Shattock, and many other experimenters.) Cancer in the mammary gland of bitches is not of rare occurrence; it completely coincides with epithelial cancer in the human subject, yet all inoculations and experiments of grafting of such cancer material on to healthy dogs have hitherto failed. But such negative results are only of relative value, since the conditions under which an individual becomes susceptible to cancer are not known, and therefore one of the essentials of a successful experiment is absent.

There exists at present a large amount of literature on the occurrence of coccidia in the epithelial cells constituting cancer; by various methods of staining, special bodies, oval and spherical, some containing what look like numbers of spores, have been described by various observers. They were noticed in Paget's 'Disease of the Nipple of the Breast,' and in other cancers. (Darrier, Albarran, Wickham, Thoma, Sjöbring. For the literature *see* Sjöbring in 'Fortschritte der Medicin,' VIII., No. 14, 1890). Russell, and particularly Podwyssozki, Jun., and Sawtschenko ('Centralbl. f. Bakter. und Parasit.,' XI., Nos. 16–18) give a very good account of these bodies, the latter also describing spores in them. According to these authors the presence of these assumed coccidia produces the epithelial multiplication for the object of supplying the parasite with a sufficient host.

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[1] *Loc. cit.*, p. 81, fig. 24.

There can be no question as to the facts described; the only question is as to whether the interpretation given by these observers, in regard to these bodies being coccidia and spores, is the correct one. The interpretation as to these bodies being parasitic in nature is perhaps not quite unjustifiable; but until their life history is better known, and until they have actually been seen in a living and growing state, i.e. in culture, and until the assumed spores have been seen to be capable of germination, it is advisable to be very cautious, without, however, denying the possibility that those bodies are really what they are said to be, viz. coccidia or something similar. In connection with this it might, however, be mentioned that bodies similar to these assumed coccidia are known to occur in the substance of epithelial and other cells under normal and various pathological conditions. Thus, Grützner noticed in certain phases of activity of certain glandular epithelial cells, the presence in the cell protoplasm, besides the typical nucleus, of a secondary nucleus-like body, probably corresponding to Balbiani's paranucleus. Other observers, again, have described in various pathological processes of epithelium in the protoplasm of the cells peculiar masses, spherical and oval, looking and staining differently from the main protoplasm. The caution enjoined by such experienced histologists as Klebs and Eberth[1] should be carefully considered by all less-experienced histologists before emphatically asserting (as is done by some) the parasitic nature of those bodies. What remarkable changes do occur in nuclei and cells, leading to the presence in the cell protoplasm of peculiar bodies, differentiated by complicated methods of staining, is well illustrated in a paper by Dr. Martin Heidenhain.[2] In Heidenhain's memoir in Plate X., bodies are shown in the cell protoplasm of leucocytes, brought out by special methods of staining, which are derived from the original cell nucleus; and, further, in Plate XI., the presence of numbers of peculiar corpuscles, which bear a striking resemblance to what the above writers on cancer consider as spores in the epithelial cells of cancer, is differentiated in the cell protoplasm; yet there can be no question that in Heidenhain's observations the bodies described and figured by him have nothing whatever to do with any intracellular parasites.

CHAPTER XXX

BLASTOMYCETES, OR TORULA

These organisms are of interest to the pathologist in two ways: (*a*) by their being constantly present in air, and consequently occurring on the skin and the surface of the mucous membranes in contact or in communication with the air; and (*b*) by a species of torula being connected with a well-defined disease, to wit, *thrush* in infants.

Torula is capable of producing alcohol when growing in substances containing glucose. By torula is understood an oval microbe varying in length between 2 or 3 μ to 5 or 6 μ, consisting of a membrane and protoplasmic contents, including one or two vacuoles. Torulas multiply not by fission but by gemmation, as shown in Plate XLI., fig. 98. They are capable of forming endocellular spores—ascospores (Rees). A large number of different species of torulas are known and have been carefully studied and cultivated by Hansen (*see* his various memoirs in the 'Berichte des Karlsberg Laboratorium'), and their ability to produce alcohol from glucose under various conditions of growth minutely studied by him.

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[1] *Fortschritte d. Med.*, VIII., No. 17.

[2] *Ueber Kern- und Zellprotoplasma*, Leipzig, 1892

Different species of torula are constantly to be found in the air, soil, drinking water, and in river and pond water; a plate of sterile gelatine, after the setting of the gelatine, exposed to air or infected with a drop of water, covered up again, and then incubated, not infrequently reveals the presence of colonies of torula, besides the usual colonies of moulds and bacteria. Amongst these torulas some species are characterised by their growth being coloured pink; at least two species of such pink torulas can be obtained from London air—one species which liquefies gelatine and one species which does not liquefy it. In the fluid of the mouth and pharynx, torulas are normally present; in the contents of the large intestine, they are normally present. In a case of diabetes from which Dr. Bedford Pierce procured urine drawn from the bladder, the freshly drawn acid urine was found uniformly turbid, owing to the presence of torulas; in fact, the urine contained a pure culture of torula, as was shown by plate and tube cultivations. This torula grew well in acid grape-sugar gelatine, and changed the sugar into alcohol; on ordinary alkaline nutrient gelatine (beef broth, peptone gelatine) it grew but slowly and not copiously, forming a whitish, grey, moist-looking growth. Pathological products of the skin and mucous membranes, i.e. those exposed to the air, contain torula; thus, for instance, vaccine lymph from the calf sometimes contains a few torula cells.

The torula species connected with alcoholic fermentation grows well on acid sugar gelatine, forming white round colonies in gelatine.

A definite species of torula, Saccharomyces mycoderma, is capable of forming acetic acid in wine, beer, and in fermenting cabbage (Sauerkraut). During its growth it forms a scum or pellicle on the surface, being dependent on the oxygen of the air. Its cells are oval, 6 μ long, 2–3 μ broad; when growing in fluids it forms spores, just like other torula species, the cells enlarging and containing, i.e. forming in its interior, the spores—ascospores (Rees).

When growing in fluids containing alcohol it oxidises the alcohol into acetic acid, and thus in its chemical action is analogous to the bacterium mentioned in a former chapter as bacterium aceti. Cienkowsky first showed that in acid nutritive fluids the cells elongate, and by gemmation produce new cells, which elongate and remain joined to the mother cell, and by the repetition of this process form threads composed of oval or cylindrical cells, the older the more elongated. In this way septate threads are formed, which, just like a mycelium of a true fungus, form branches. A torula, morphologically identical with this, is the species known as oïdium albicans, and as being the active cause of thrush (Plate XL., fig. 100). Grawitz,[1] who worked this out satisfactorily, has traced it through all phases of growth, and has also shown that, like other saccharomyces, it forms ascospores. It grows well on nutritive gelatine, and in streak cultivation forms a greyish-white fluffy growth, in which the formation of threads is actively going on.

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[1] *Virchow's Archiv*, Band LXX.

CHAPTER XXXI

MOULDS, OR MYCELIAL FUNGI

THIS group comprises microbes which consist of cells multiplying by fission, and which by continued linear and lateral multiplication, and by elongation, form branched mycelial threads; each of these is composed of cylindrical cells. The ripe cells consist of a cellulose sheath, and within is a homogeneous substance, or rather the remains of a faintly granular protoplasm, filled with or replaced by clear vacuoles. The cells are separated from one another by a transverse septum of cellulose. The young and growing threads, both terminal and lateral, do not show septa, but have their sheaths filled with a uniform slightly granular protoplasm not segmented into separate cells; the ends of such threads are rounded.

In some species the terminal threads by a process of simple fission of their protoplasm produce oblong or spherical cells, which ultimately become altogether separated from one another and free; these cells are the conidia or spores. Such species are spoken of as oïdium, of which there are known several, e.g. oïdium lactis, oïdium of favus (Achorion Schönleinii), oïdium of ringworm (Trichophyton tonsurans), and of pityriasis versicolor (Microsporon furfur). In these species no other mode of the formation of spores has yet been ascertained. The spores by germination elongate, and by continued growth and subsequent division and septation give rise to the branched mycelium composed of cylindrical cells.

But there exist fungi, like Aspergillus, Mucor, and Penicillium, which, while growing under suitable conditions, particularly when growing on a surface exposed to free air, show a more complex mode of spore formation; but which, when growing in a fluid medium and not exposed to free air, behave like an oïdium, that is to say, they form spores by simple fission of the protoplasm of the terminal portions of the mycelial threads.

Oïdium lactis forms on milk, bread, paste, potato, gelatine, &c., a whitish filamentous growth; its spores are spherical or oval, measuring 7–10 μ (Plate XL., fig. 99).

The *oïdium of favus*, and that of herpes, of ringworm, and of pityriasis versicolor behave in morphological and cultural characters very much like the oïdium lactis.[1] Just as in this, the spores are spherical or oval, 7–10 μ in length, and when germinating, elongate, and by repeated division form branched septate mycelial threads; the terminals of these form chains or clusters of spores. On agar and on gelatine the growth has a white colour, and appears fluffy (Plate XLI., fig. 101).

In ringworm, one of the loose hairs examined in liquor potassæ shows the spores in multitudes on the surface of the hair, and between the cells constituting the hair substance. A fresh hair of a ringworm patch is placed in melted nutrient agar; this is shaken and then poured out on a plate for plate cultivation. After several days' incubation at 37° C. numerous colonies of the oïdium fungus pervade the agar. In order to avoid as much as possible accidental bacteria, it is best to make from the first tube, after inoculation and shaking, a second inoculation, that is to say, by inoculating with a platinum loop a second tube of agar, and use this for a plate cultivation. The number of oïdium colonies will be found limited, and bacterial colonies probably altogether absent.

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[1] Grawitz, *Virchow's Archiv*, Band LXX., p. 560.

Aspergillus.—The spores of species of Aspergillus abound in air, water, in the mucus of the nasal cavity, in the fluid of the mouth, and in most substances exposed to air and subjected to putrefaction.

During the growth of the mycelium some of its branches assume an upright position, are thicker and not at all, or only slightly septate, and at their free end form a flask-shaped enlargement, from which grow out radially thin cylindrical cells—*basidia*. These at their distal or free end produce a chain of spherical spores or conidia (Plate XL., fig. 104). This is a very common mould, and according to differences in the colouration of the mycelium and spores is subdivided into different species: *A. glaucus, candidus, flavescens, fumigatus, niger*, &c.

Besides this mode of spore formation (asexual), there is another (sexual), which according to De Bary consists in this: some terminal branch of the mycelium becomes twisted like a spiral; this is considered to be the female organ of fructification or *carpogonium*; from the same thread branches grow towards the carpogonium; one of these branches becomes fused with the terminal portion of the carpogonium called the ascogonium, while the others, the *pollinodia*, branch and surround the carpogonium like a capsule; the whole organ is now called a *perithecium*. Finally, the ascogonium by rapid division gives origin to a number of oval septate tubes, inside which by endogenous formation numerous spores make their appearance.

Grohe [1] was the first to show that the introduction of the spores of some species of Aspergillus into the vascular system of rabbits sometimes produces death, with symptoms of metastasis into the various organs, due to localised foci, where these spores grow into mycelial filaments. Lichtheim [2] showed that such mycoses in rabbits cannot be produced by the spores of *Aspergillus glaucus*, but easily by those of *Aspergillus flavescens* and *fumigatus*, in less degree by *Aspergillus niger*. Grawitz [3] studied this process more minutely, and found that, whether the spores are injected into the vascular system or into the peritoneal cavity, there are established in the kidneys, liver, intestines, lungs, muscles, and occasionally in the spleen, long bones, lymphatic glands, nervous system, and skin, minute metastatic foci, due to the growth of the spore into mycelial filaments, with imperfect organs of fructification, but no spore formation. Grawitz thought that the spores of ordinary moulds (Penicillium and Aspergillus) are capable of assuming these pathogenic properties if cultivated at higher temperatures (39–40° C.) and in alkaline media. These fungi, as is well known, grow well at ordinary temperatures and in acid media, and are then innocuous when introduced into the animal body; but by gradual acclimatisation they can also be made to grow at higher temperatures and in alkaline media, when they assume pathogenic properties, becoming capable of resisting the action of living tissues and of growing in them. This view has been proved to be incorrect by Gaffky,[4] Koch,[5] and Leber.[6] Those spores that do exert such pathogenic properties are not at all dependent on such acclimatisation, and are not ordinary moulds, but distinct species of Aspergillus (Lichtheim), which grow well at higher temperatures—such as 38–48° C.—and the spores of which under all conditions of growth are capable of producing in rabbits the mycosis in question.

Penicillium.—This fungus has also a wide distribution, but is not so common as Aspergillus. In Penicillium as in Aspergillus, hyphæ, which are not septate, grow out from the mycelium; from the end of each of these hyphæ arise like the fingers of the hand a number of short, branched, cylindrical cells, each of which gives origin to chains of spherical spores (*see* Plate XLI., fig. 102). Of this no pathogenic species are known.

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[1] *Berl. klin. Woch.*, 1871.

[2] *Ibid.*, IX. and X., 1882.

[3] *Virchow's Archiv*, Band LXXXI., p. 355.

[4] *Mittheil. a. d. k. Gesundheitsamte*, 1880.

[5] *Berl. klin. Woch.*, 1881.

[6] *Ibid.*, 1882.

Mucor occurs on many substances subject to putrefaction, but is less common than either of the two preceding; it is characterised by this, that from the mycelium, non-septate hyphæ grow out, at the end of which a spherical enlargement appears, *sporangium*, in which by endogenous formation a large number of spherical spores are developed; the wall of the sporangium giving way, the spores become free (*see* Plate XLI., fig. 103).

Lichtheim[1] describes two species, which possess pathogenic action, Mucor rhizopodiformis and Mucor corymbifer (*see* Plate XLI., fig. 103). The mycelium of the former is at first white, then changes to grey; that of the latter is always whitish-grey. Both species were found growing on wheat bread kept at higher temperatures (37° C.). Spores of either, injected into the vascular system of rabbits, produce death in forty-eight to seventy-two hours. On *post-mortem* examination the Peyer's patches of the ileum are found intensely congested, swollen, and even ulcerated; in these, as also in the swollen and congested mesenteric glands and in the kidneys, mycelial growths are present. Both these species grow luxuriantly at the body temperature.

An important case of general '*mycosis mucorina*' in man, ending in death, has been described by Dr. Paltauf.[2] From the alimentary canal of the patient an invasion of the internal organs by the mycelium and spores of a species of Mucor occurred, leading to the formation of metastatic inflammatory foci in the Peyer's glands, lungs, pharynx, larynx, cerebrum, and cerebellum. In all these organs were found smaller and larger foci of inflammation, caused by the presence of non-septate branched mycelial threads and sporangia, showing that the fungus belonged to the group of Mucor.

Saprolegnia (Plate XLI., fig. 107)—colourless tubular threads, forming gelatinous masses on living and dead animal and vegetable matter in fresh water. The cylindrical or flask-shaped ends of the threads, *zoosporangia*, form in their interior numbers of spherical or oval spores, *zoospores*, possessed of locomotion (one flagellum at each pole), and which finally escape from the threads. These zoospores after some time become resting spores, surround themselves with a membrane, and finally germinate into a cylindrical mass which becomes transformed in the mycelium. Besides this asexual, there is a second or sexual mode of fructification, consisting in this: At the end of a mycelial thread a cell grows up into a spherical large ball, the *oogonium*. From the same thread, thin threads, *antheridia*, grow towards the oogonium, into the protoplasm of which they merge. This latter then differentiates into a number of spherical masses, the *oospores*, which become invested with a membrane; these become free and then germinate and grow into a mycelium. Saprolegnia grows on the skin of living fish, and causes here severe illness, often terminating in death. Thus the salmon disease, as Professor Huxley has shown,[3] is caused by this parasite. The zoospores of this salmon saprolegnia are, however, as Huxley has shown, as a rule, non-motile. The hyphæ of the fungus traverse the epidermis in the diseased patches of the salmon, and they bore through the superficial layer of the derma, a stem part being situated in the epidermis, and a root part in the derma; each of these elongates and branches out. 'The free ends of the stem hyphæ rise above the surface of the epidermis, and become converted into zoosporangia, more or fewer of the spores of which attach themselves to the surrounding epidermis and repeat the process of penetration.' In Saprolegnia associated with the salmon disease, Professor Huxley observed only the asexual mode of fructification.

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[1] *Zeitschrift f. klin. Med.*, Band VII., Heft 2.

[2] *Virchow's Archiv*, Band CII. and CIII., p. 543.

[3] *Proceedings of the Royal Society*, 1882, No. 219.

Plates I–XVII inclusive—figures 1 to 118 (except figures 45, 46, 69, and 86)—are from micro-photograms by A. Pringle and E. C. Bousfield. Except when otherwise stated, the magnifying power is 1,000.

PLATE I

Fig.

1. Cover-glass specimen from a culture of staphylococcus albus liquescens . . . . A. P.

2. From a culture of a sarcina-like staphylococcus . . . . A. P.

3. From a culture of sarcina lutea . . . . E. C. B.

4. From a specimen of micrococcus tetragonus . . . . . A. P.

5. Micrococcus scarlatinæ, from a culture on gelatine . . . A. P.

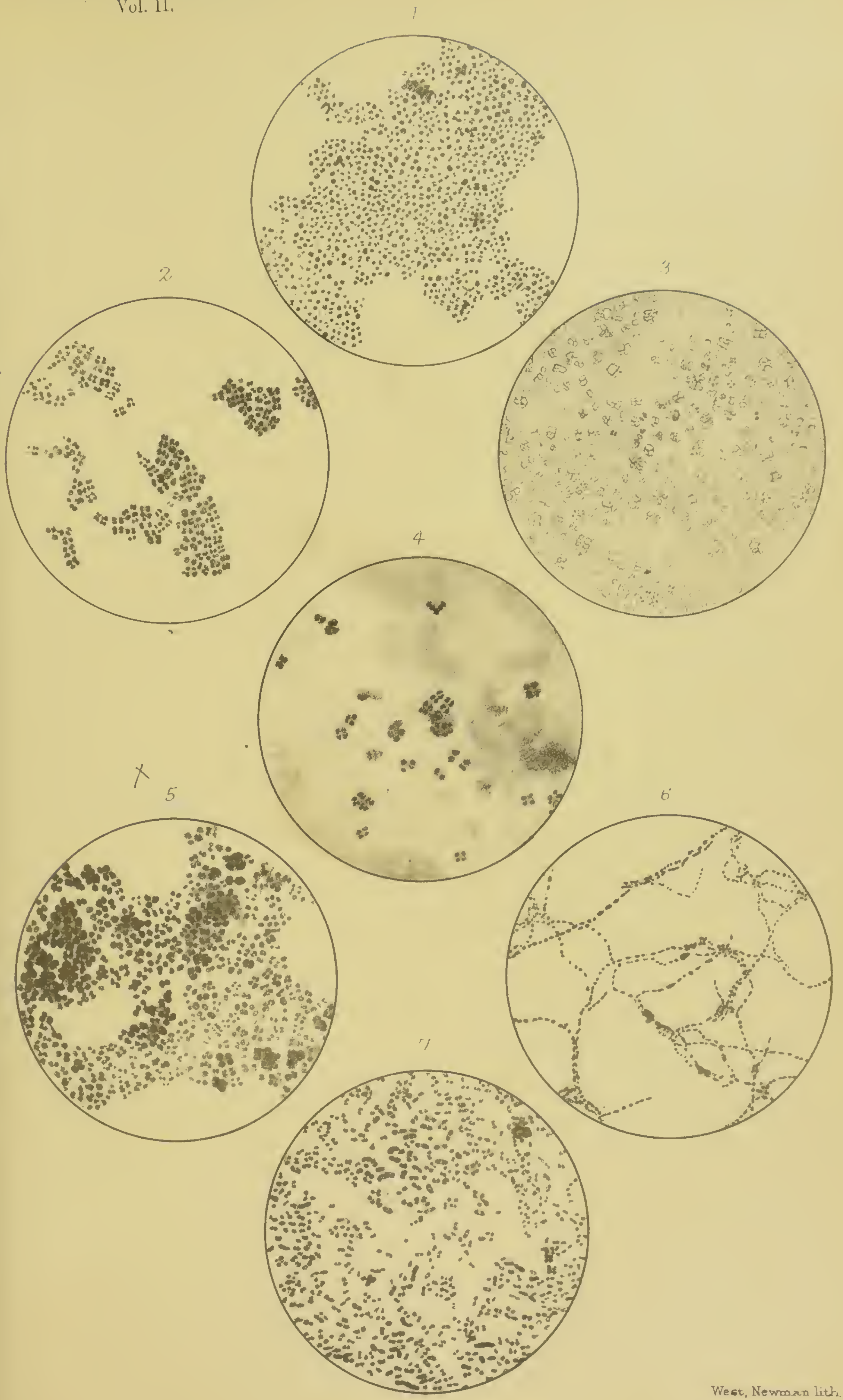
6. From a cultivation of bronchial sputum of influenza, showing chains of short rods, many of these resembling a diplococcus . . . A. P.

7. From a culture of a short oval bacillus from veal pie that had caused choleraic diarrhœa. The bacilli are marked as short ovals, each with polar granules . . . . A. P.

[Treatise on Hygiene.]
Vol. II.

Pl I.

[Klein]



West, Newman lith.

PLATE II

FIG.

8. From a cultivation of bacillus of grouse disease obtained from an infected mouse. Amongst the short oval forms there are some which are more distinctly cylindrical bacilli . . . . A. P.

9. From a cultivation of a proteus-like bacillus obtained from pork which had caused choleraic diarrhœa in Carlisle . . . . . A. P.

(All forms between cocci and long threads are present. × 650.)

10. From very young colonies on gelatine of proteus vulgaris, as seen under a low power. The ‘swarmers’ passing out from the colonies are well seen . . . . A. P.

11 and 12. From the same specimen as fig. 10 magnified 1,000. The thread-like character of the bacilli is well shown . . . . . A. P.

13. From a plate culture of bacillus mesentericus on gelatine. The figure represents the margin of a young colony . . . . . . A. P.

14. Bacillus filamentosus from a gelatine culture of sewage. The cylindrical nature of the bacilli constituting the chains and threads is well shown. A. P.

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Vol. II.

Pl. II.

(Klein)

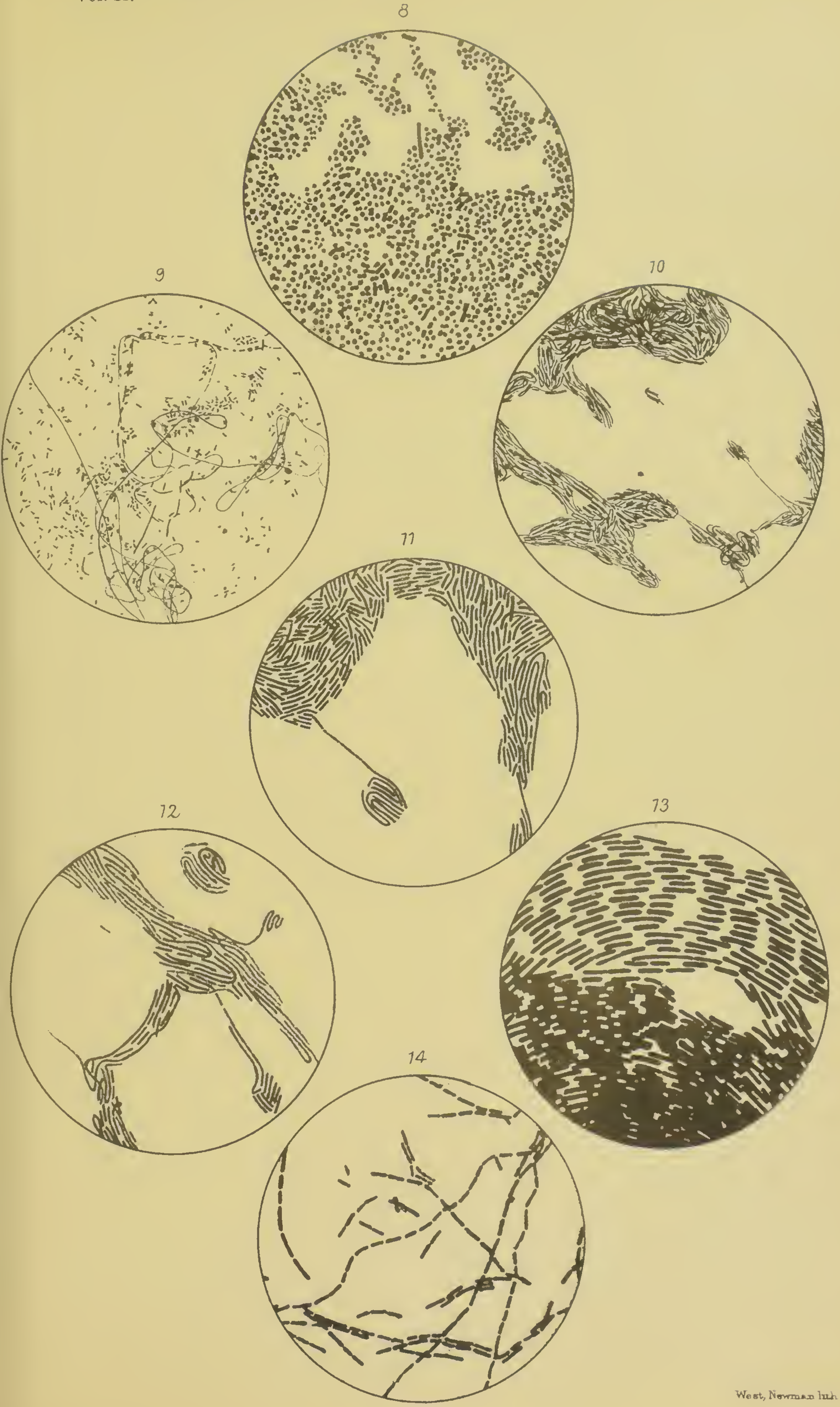

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PLATE III

FIG.

15. From a gelatine culture of bacillus anthracis two days old; some of the threads show the constituent bacilli as spherical or oval torula-like forms . . . . A. P.

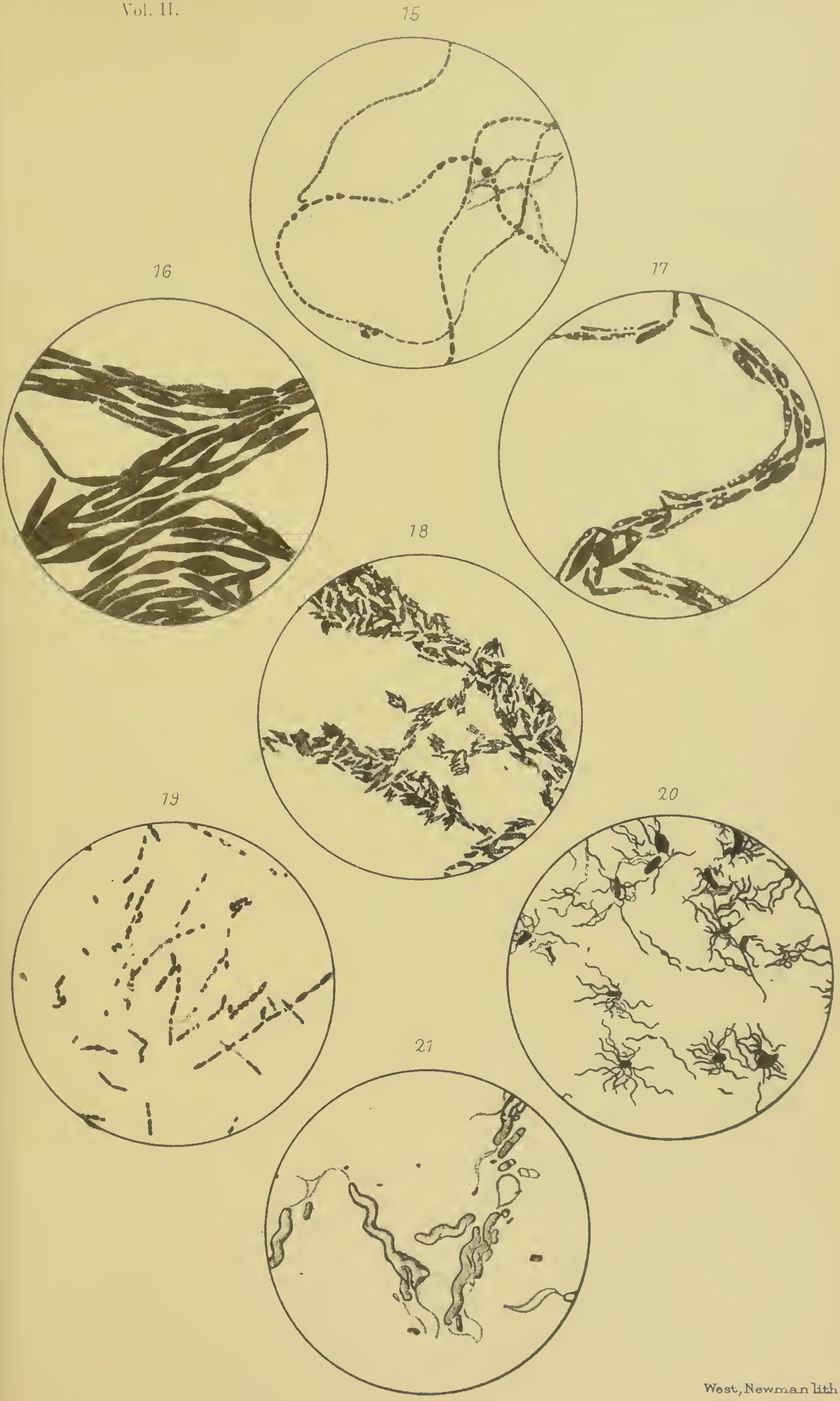
16 and 17. From a recent gelatine plate cultivation of bacillus anthracis. The bacillary threads are composed of spindle-shaped elements, many of them containing small vacuoles . . . . A. P.

18. From a culture on gelatine of a non-liquefying, extremely minute bacillus that had been found in dust of a room. Each bacillus contains in its middle an oval spore . . . . A. P.

19. From a culture of bacillus filamentosus, the threads containing oval spores . . . . A. P.

20. From a gelatine culture of the typhoid bacillus, each bacillus being possessed of numerous flagella . . . . E. C. B.

21. Spirilla, each with two flagella at one end . . . . . . A. P.



West, Newman lith

PLATE IV

Fig.

22. From a culture in gelatine of the comma bacillus of Finkler . A. P.

23. Purulent matter of abscess of rabbit, numerous cocci . . . A. P.

24. Purulent matter of abscess of the human mastitis . . . A. P.

25. Streptococcus scarlatinæ from an agar culture . . . . A. P.

26. Streptococcus scarlatinæ from culture . . . . . . A. P.

27. Streptococcus of foot-and-mouth disease, culture . . . . A. P.

28. Bacillus pyocyaneus, culture . . . . . . E. C. B.

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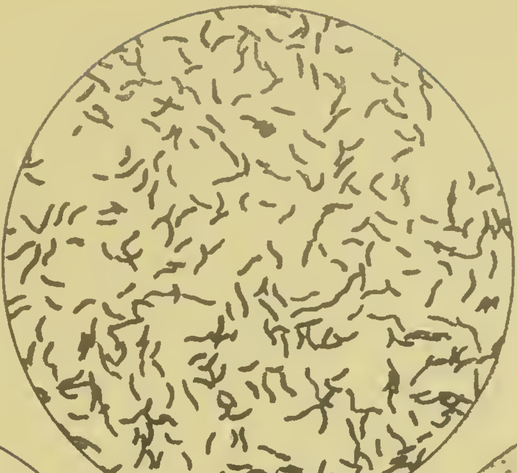

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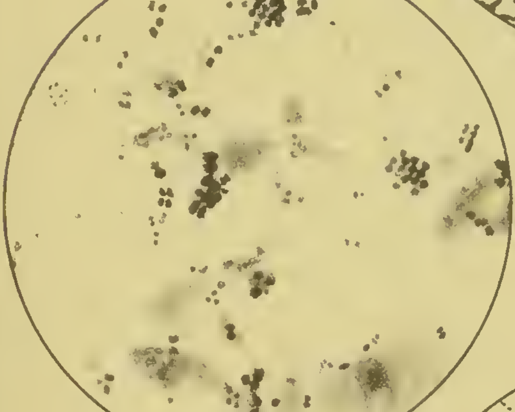

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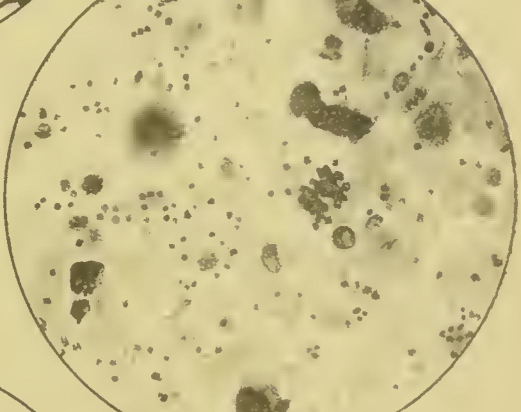

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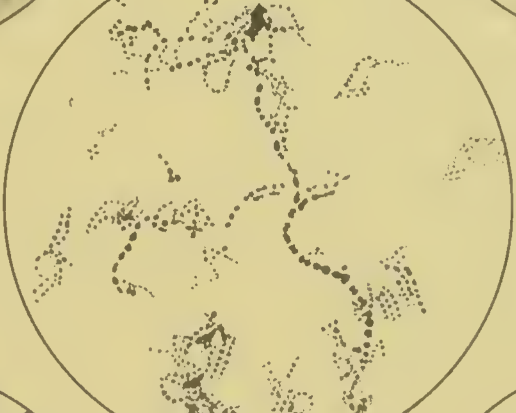

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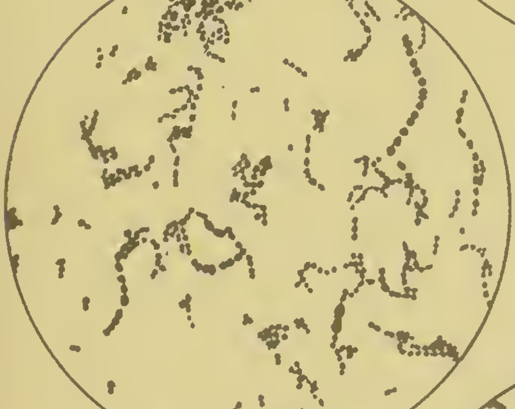

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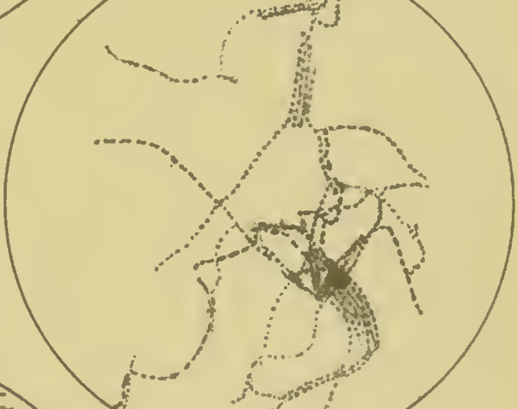

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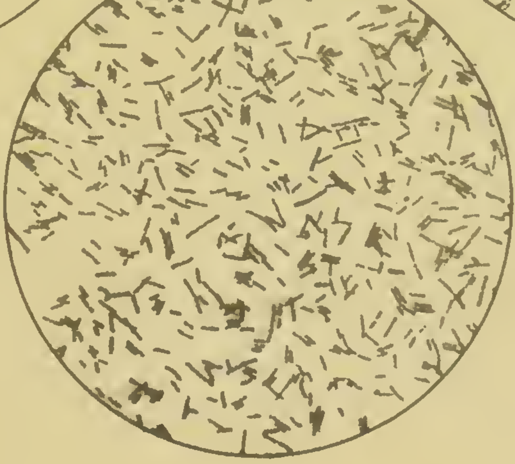


West, Newman lith

PLATE V

Fig.

29. Section through human variola, showing the loculi forming the vesicle. Low power . . . . A. P.

30. Section through the inoculated pock of sheep, showing the loculi forming the vesicle. Low power . . . . A. P.

31. Section through the natural eruption of foot-and-mouth disease in the sheep, showing the nature and formation of the vesicle in the epidermis. Low power . . . . E. C. B.

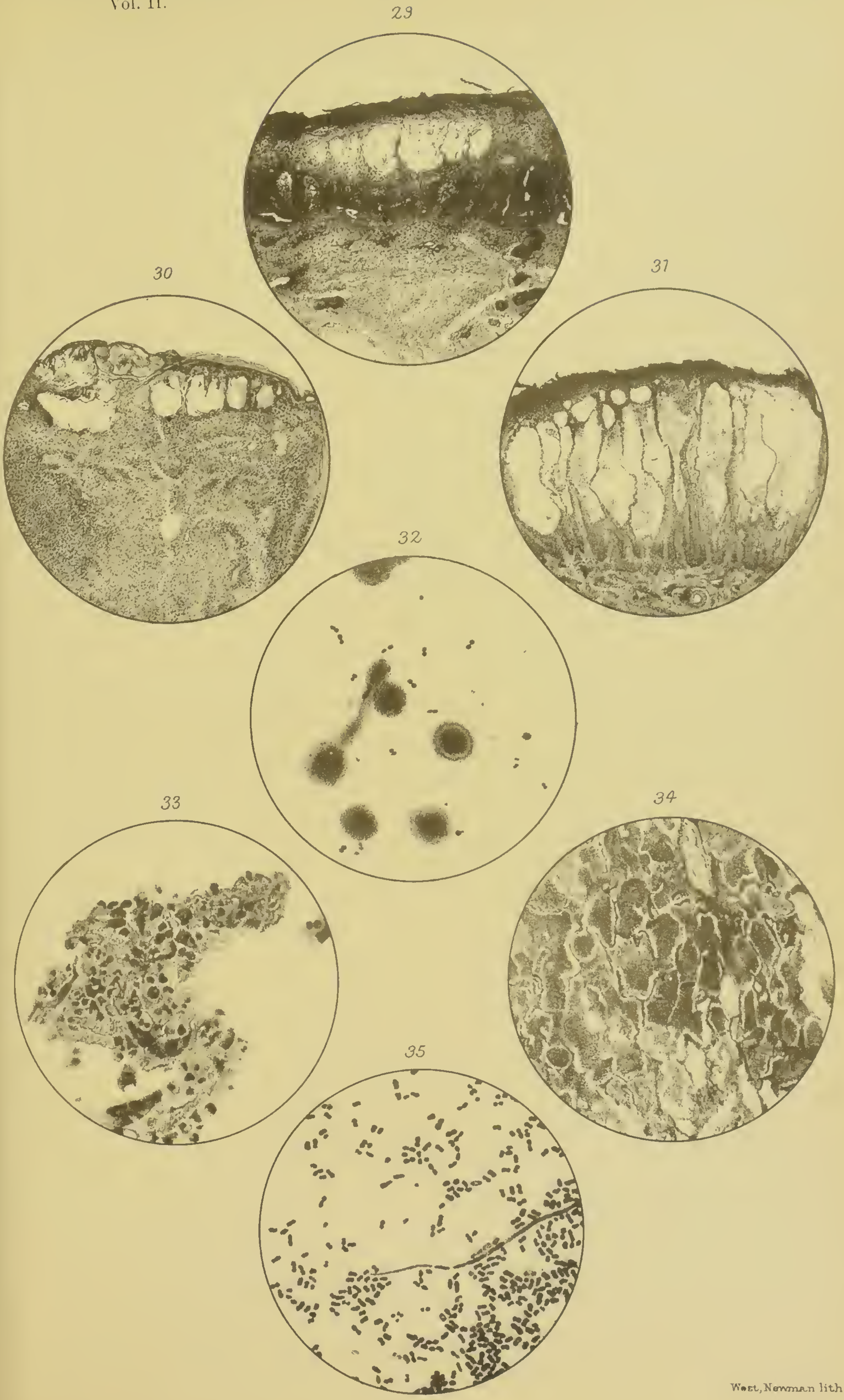
32. Cover-glass specimen of the lung juice in croupous (Middlesbrough) pneumonia. Amongst the red blood discs, there are numerous short bacilli, single and as diplo bacilli . . . . . . A. P.

34. Section through the lung in the stage of red hepatisation in croupous (Middlesbrough) pneumonia; the alveoli of the lung are filled with fibrin and red blood discs. Low power . . . . . A. P.

33. From the same lung, more highly magnified. ×650 . . . A. P.

35. Cultivation of the bacillus pneumoniæ (Middlesbrough) . . . A. P.

Pl V.



West, Newman lith.

PLATE VI

Fig.

36. Blood of mouse infected with the bacillus pneumoniæ . . . A. P.

37. Bacillus (capsulated) of Friedländer in pneumonic sputum . . A. P.

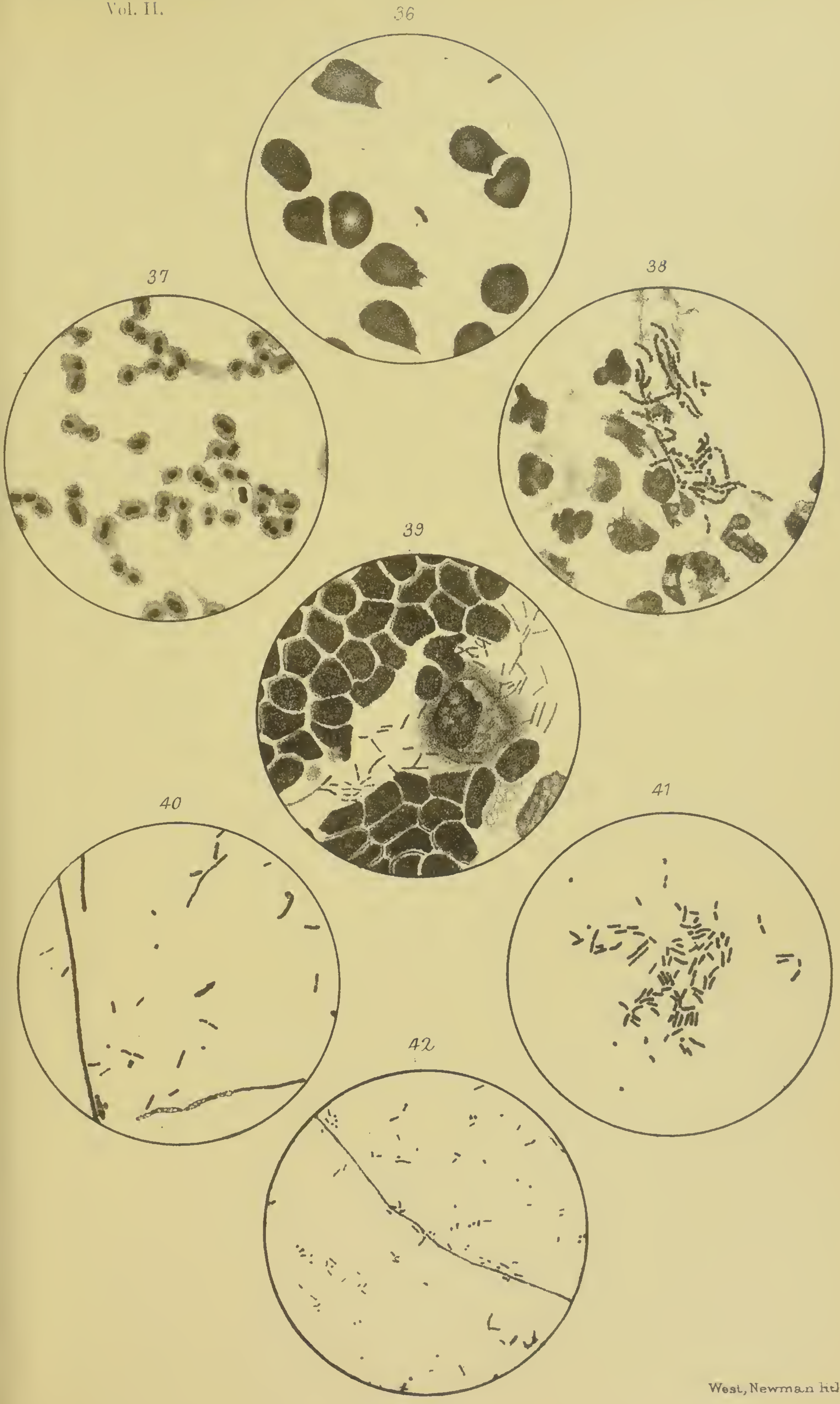
38. Streptococcus pyogenes in chronic abscess. Amongst the pus cells, chains of the streptococcus are shown . . . . . . E. C. B.

39. Blood of mouse dead of Koch's mouse septicæmia . . E. C. B.

40. Œdema fluid of a guineapig dead of malignant œdema, after inoculation with garden earth . . . . E. C. B.

41. Œdema fluid of rabbit dead after inoculation with the aërobic bacillus of malignant œdema . . . . E. C. B.

42. Culture in broth of the aërobic œdema bacillus . . . E. C. B.



West, Newman lith.

PLATE VII

FIG.

43. Section through the subcutaneous tissue of a guineapig dead after inoculation with the aërobic œdema bacillus . . . . E. C. B.

44. Œdema fluid of a guineapig dead after inoculation with (Koch's) anaërobic œdema bacillus . . . . . . E. C. B.

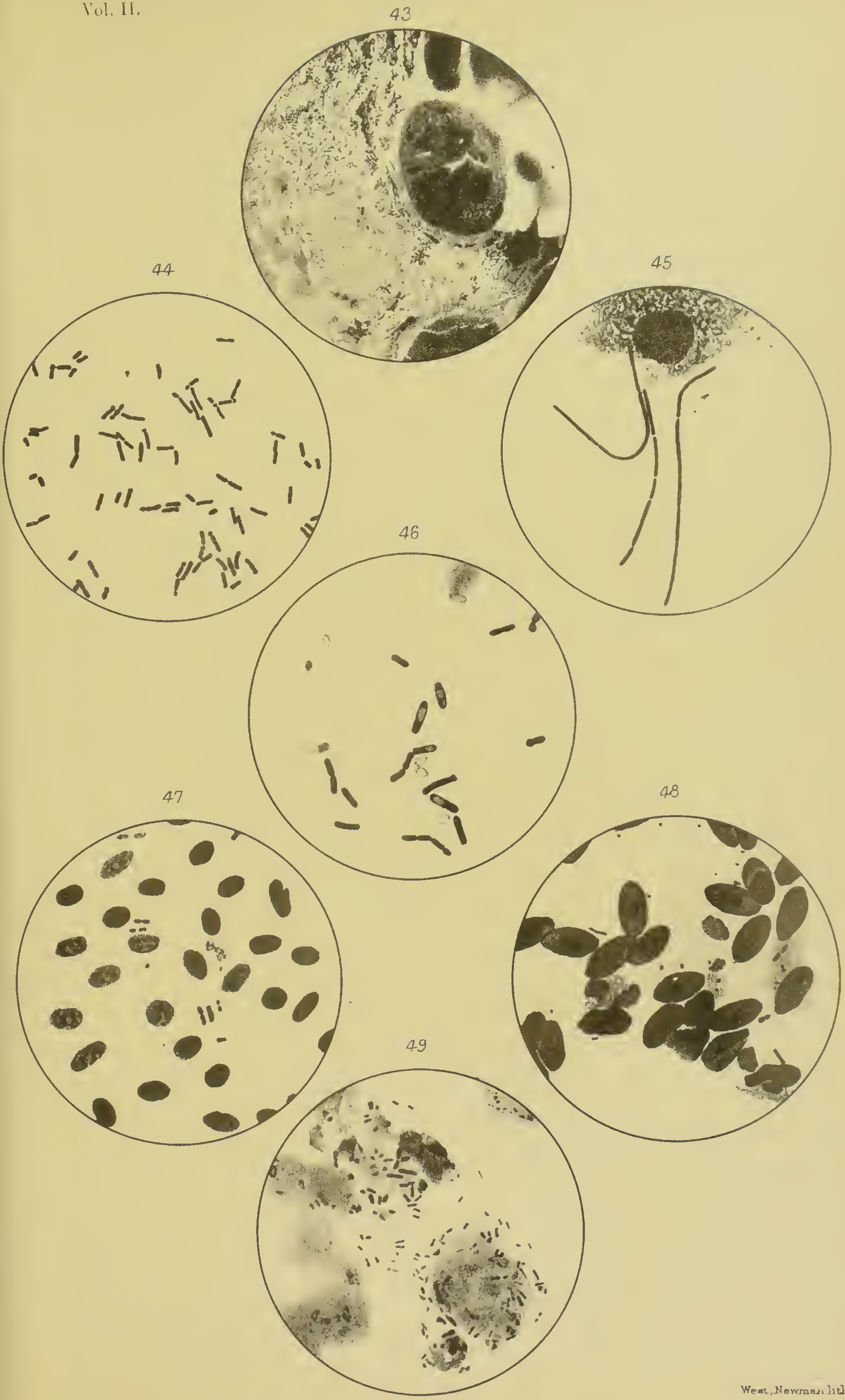
45. Copied from Fränkel and Pfeiffer's Atlas, Plate XXIII, fig. 45. Cover-glass specimen of tissue juice of a guineapig dead after infection with garden earth. Magnifying power, 1,000.

46. Copied from Fränkel and Pfeiffer's Atlas, Plate XXIV, fig. 48. Spore formation in the bacilli of a culture in agar. Magnifying power, 1,000.

47. Blood of grouse dead of the grouse disease, showing the bacilli amongst the blood corpuscles, of which only the nuclei are shown . . A. P.

48. Bacillus of grouse disease in the blood of ammer, dead after inoculation with culture . . . . A. P.

49. Blood of guineapig infected with culture of the bacillus of grouse disease. The bacilli are very numerously present, either free in the plasma or enclosed in white blood cells, the latter swollen up and disintegrating . . . . A. P.



West, Newman lith.

PLATE VIII

Fig.

50. Blood of fowl dead of fowl enteritis; very few bacilli amongst the red blood discs . . . . A. P.

51. Intestinal mucus of fowl dead of fowl enteritis. The bacilli are present in almost pure culture . . . . A. P.

52. From a culture of the bacillus of fowl enteritis . . . . A. P.

53. Blood of fowl dead of fowl cholera. The minute oval bacilli are very abundant amongst the blood discs. The bacilli show the characteristic staining of polar granules . . . . A. P.

54. Blood of rabbit dead of fowl cholera . . . . . . A. P.

55. Cultivation of the bacillus of fowl cholera . . . . . A. P.

56. Bacillus of swine fever, from the spleen of a mouse dead after inoculation . . . . A. P.

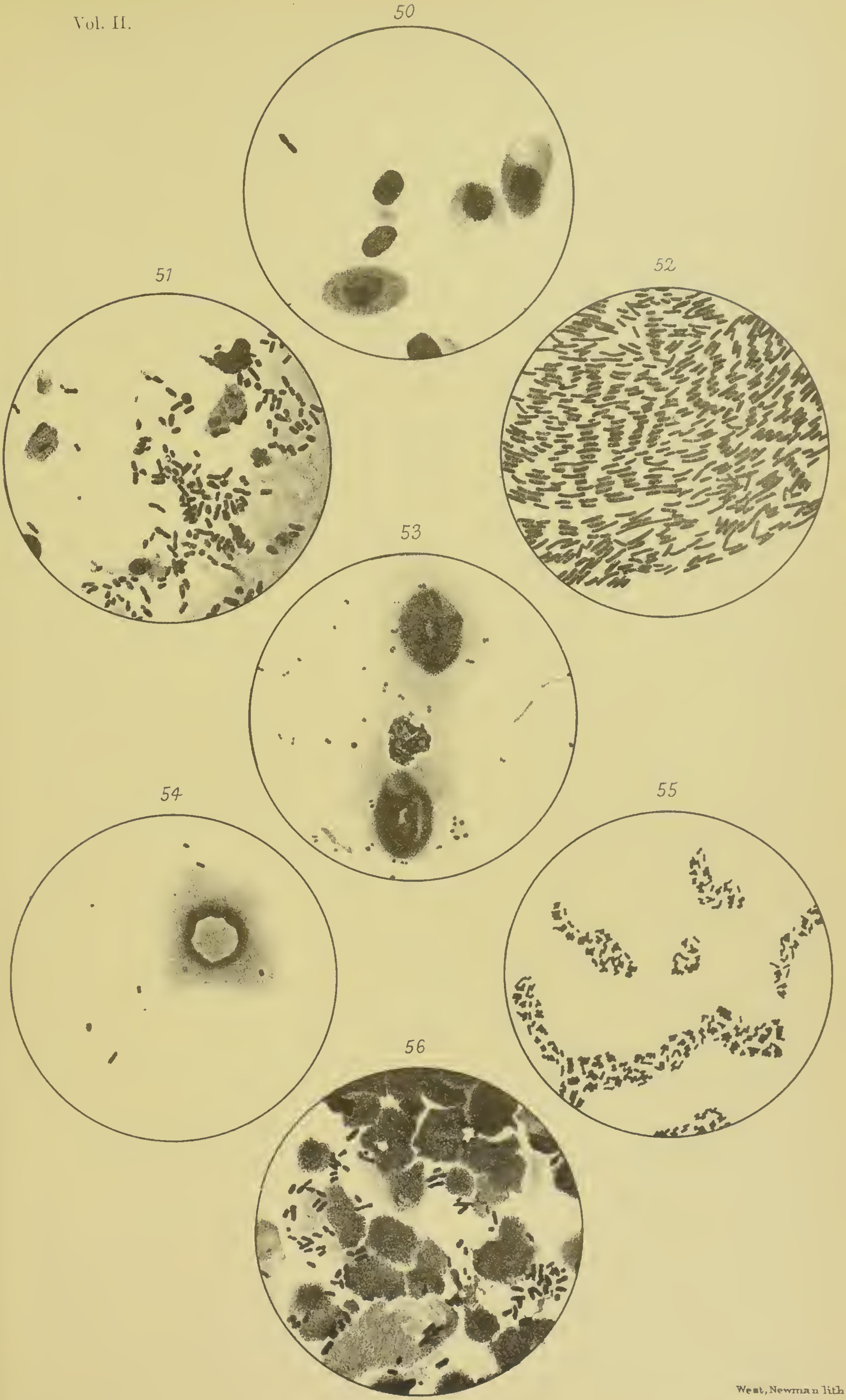


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PLATE IX

FIG.

57. Blood of pigeon dead after inoculation with culture of the bacillus of swine erysipelas . . . . E. C. B.

58. Section through the liver of pigeon dead of swine erysipelas. In the capillary blood-vessels leucocytes are seen, the interior of which is filled with the bacilli . . . . E. C. B.

59. Blood of guineapig dead of virulent anthrax . . . . A. P.

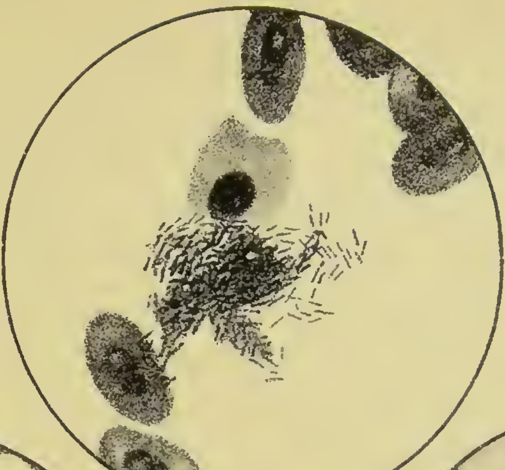
60. Bacillus anthracis from the subcutaneous tissue at the seat of inoculation of rabbit. Many chains of the bacilli show the protoplasm degenerated, and only the sheath as a pale, faintly stained thread.

61. Section through the spleen of a guineapig dead of anthrax. × 650. E. C. B.

62. Part of glomerulus of a Malpighian corpuscle in the kidney of rabbit dead of virulent anthrax. Some of the capillary blood-vessels are filled with the bacilli anthracis. × 650 . . . . . A. P.

63. Section through the liver of a guineapig dead of anthrax. The capillary blood-vessels contain abundantly the bacilli anthracis. × 650 A. P.

57



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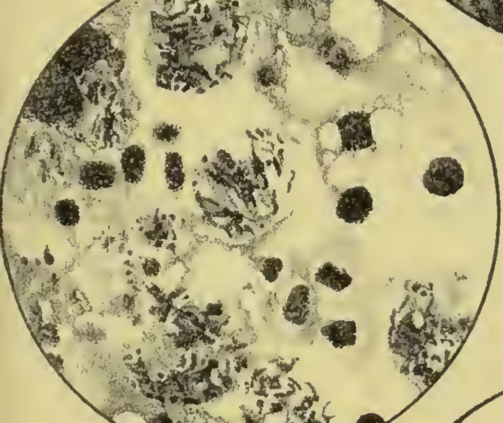

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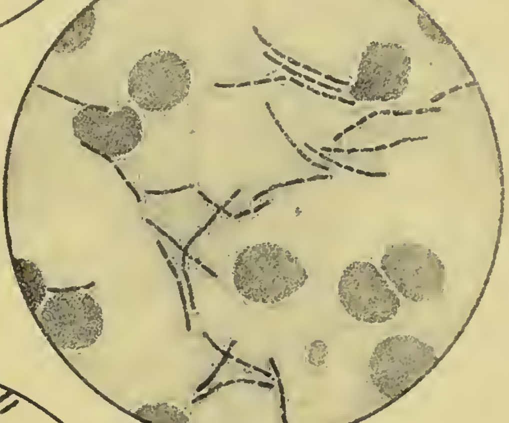

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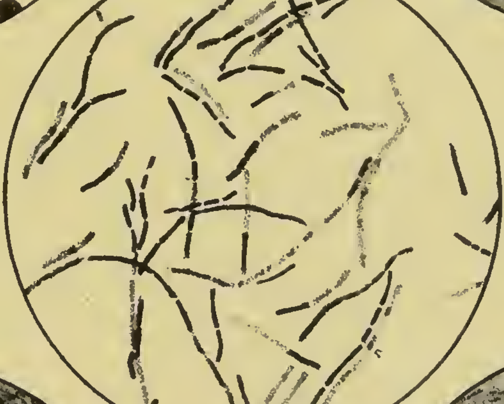

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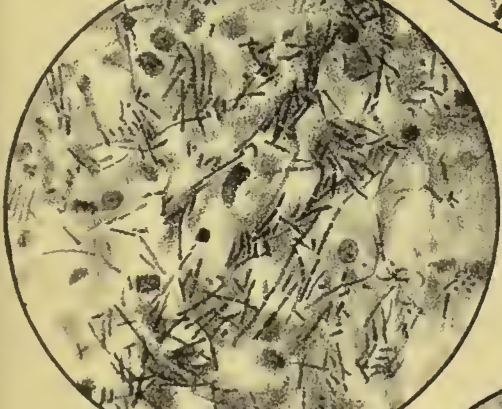

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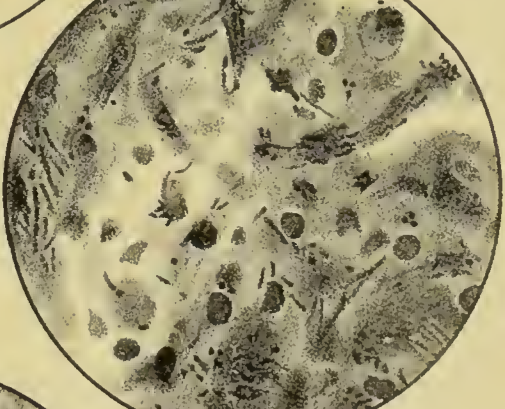

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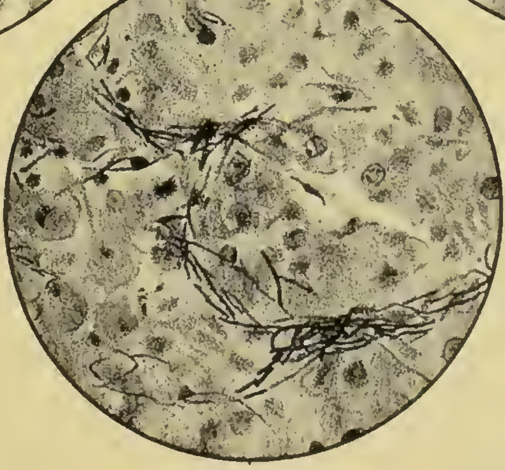


West, Newman lith.

PLATE X

FIG.

64. From a section through a human malignant pustule. A vesicle is shown between the epidermis and the corium; the vesicle is filled with fibrin; the corium is full of the bacilli anthracis. Low power. E. C. B.

65. From a similar preparation as the preceding figure. The vessels of the corium are filled with the bacilli anthracis. Low power . E. C. B.

66. Impression of a colony of bacilli anthracis on gelatine. The colony is composed of threads of the bacilli. Low power . . . A. P.

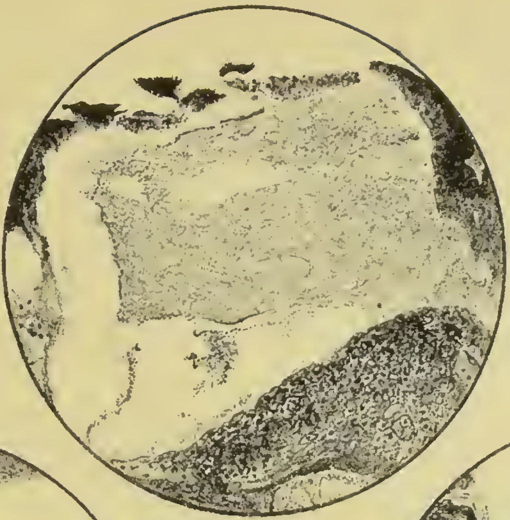
67. From a similar preparation as fig. 66, more highly magnified, showing the threads composed of cylindrical bacilli. M. P. 650 . . A. P.

68. From an impression preparation of the margin of a colony of bacillus anthracis growing in a gelatine plate. The bacilli were derived from the blood of frog infected with anthrax during narcosis; the characteristic threads are composed of cylindrical bacilli . E. C. B.

69. Threads of bacilli anthracis with spores in them in the fresh condition. The spores are the oval bright corpuscles contained in the pale threads. Copied from Koch.

70. Threads of anthrax bacilli from a gelatine culture. Many bacilli constituting the threads are swollen up into spherical, oval, or spindle-shaped elements . . . . A. P.

64



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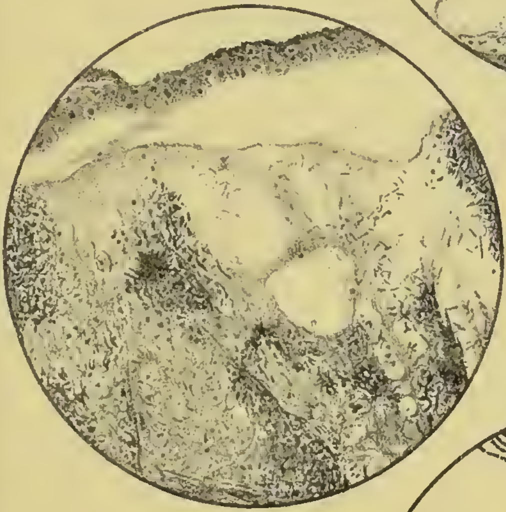

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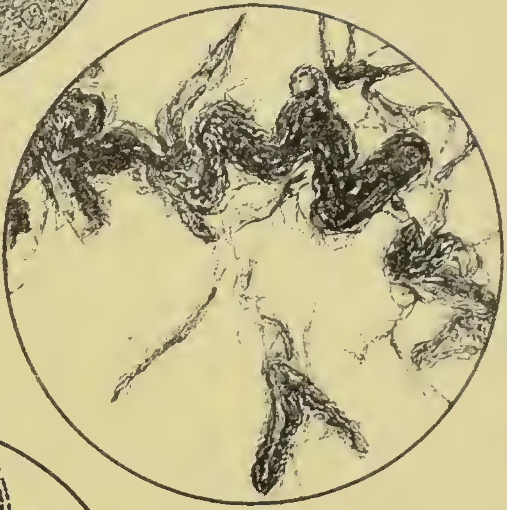

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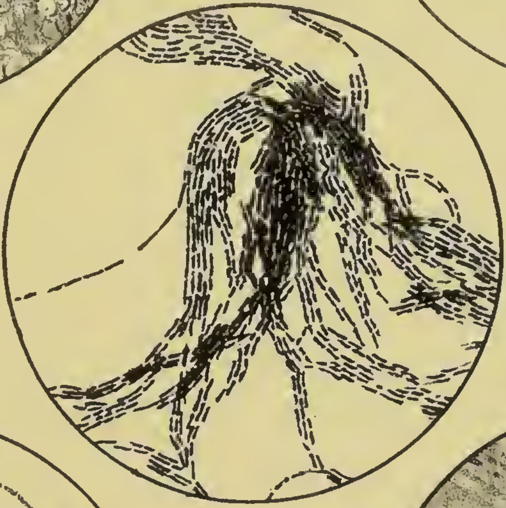

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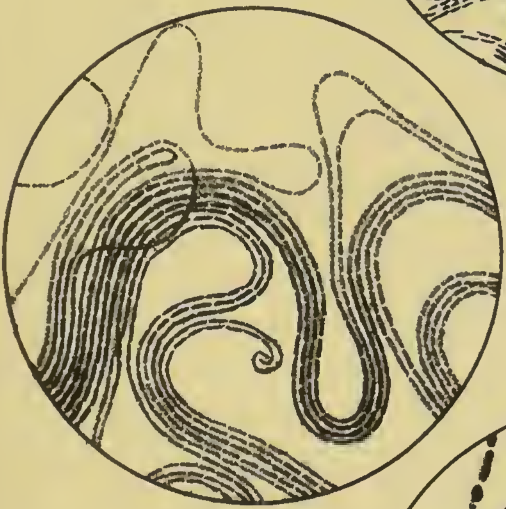

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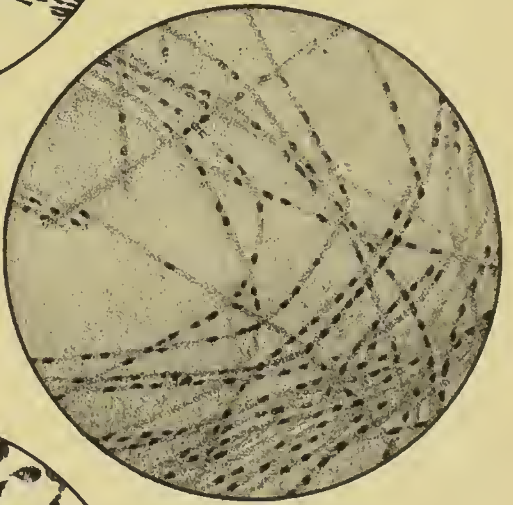

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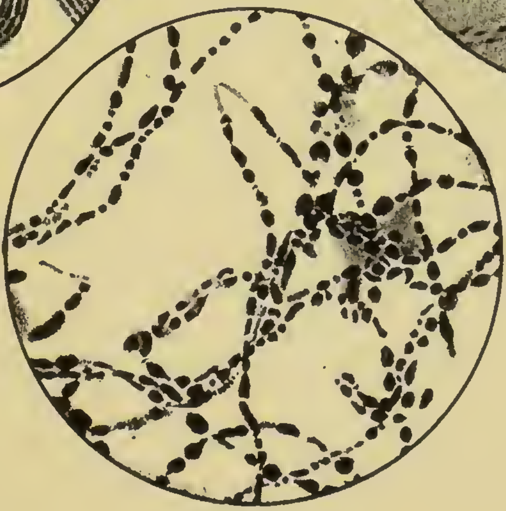


West, Newman lith

PLATE XI

FIG.

71. Blood of a guineapig dead after inoculation with symptomatic charbon. Long bacilli (chains) are seen amongst the blood discs . . A. P.

72. From the false membrane of human diphtheria of the fauces. Numerous diphtheria bacilli are seen amongst the tissue elements . . A. P.

73. From a similar preparation. Amongst the tissue cells are seen the diphtheria bacilli in almost pure culture . . . . . A. P.

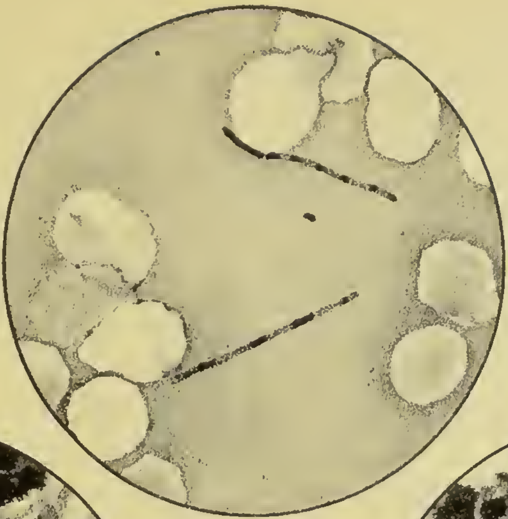
74. From a colony of an agar culture of the bacillus diphtheriæ, many bacilli single or in chains, some club-shaped . . . . A. P.

75. From an agar streak culture of the bacillus diphtheriæ . . A. P.

76. From a colony on gelatine of the bacillus diphtheriæ. The bacilli are, in many instances, conical . . . . A. P.

77. From an agar culture of the bacillus diphtheriæ derived from the necrotic tumour at the seat of inoculation of a cow inoculated with the human bacillus diphtheriæ. The bacilli are slightly smaller than those derived directly from the human . . . . A. P.

71



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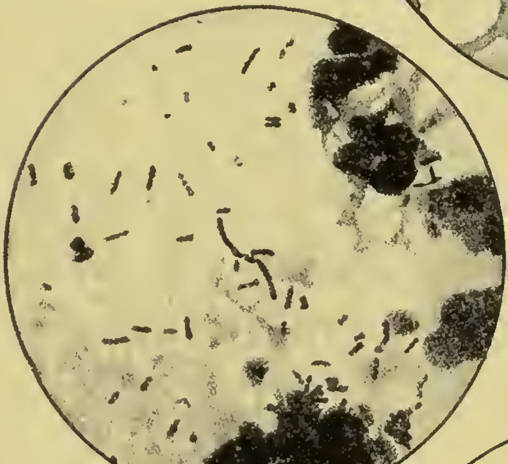

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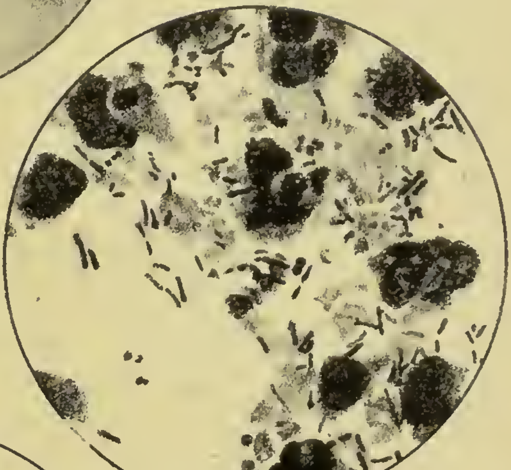

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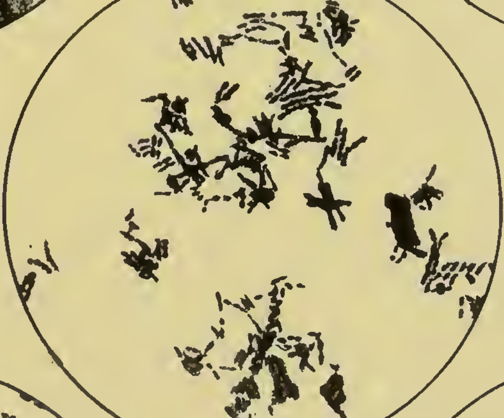

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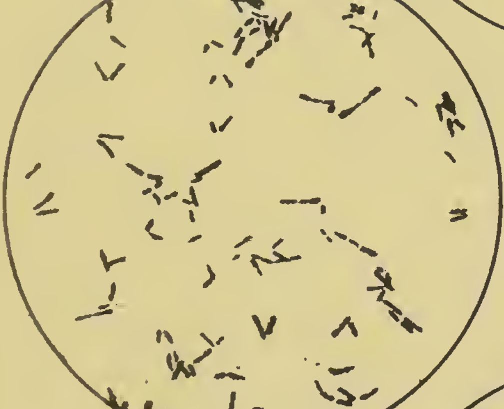

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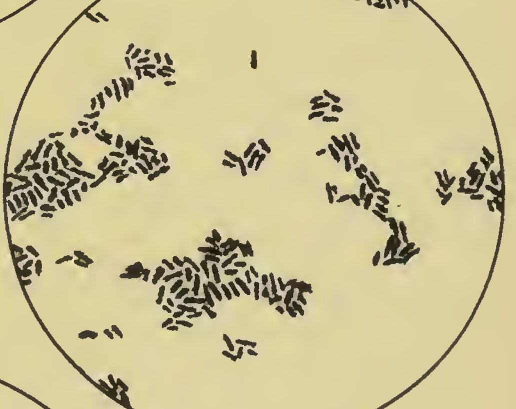

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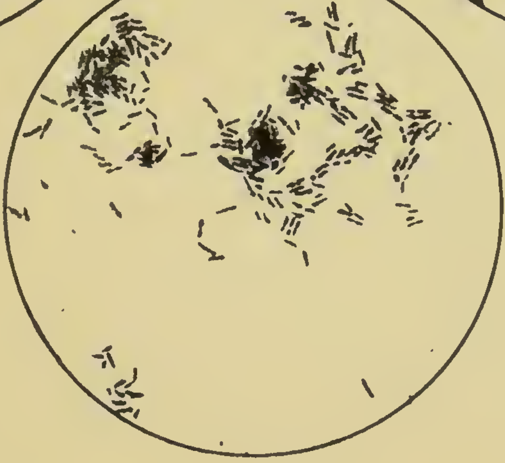


West, Newman lith.

PLATE XII

FIG.

78. From a culture of the bacillus diphtheria derived from the corneal ulcer of cat inoculated on the cornea with diphtheritic membrane. The bacilli are distinctly smaller than those of the cow or human . A. P.

79. From a gelatine culture of the milk of a cow infected by subcutaneous inoculation with the human bacillus diphtheriæ. The characteristic club-shaped bacilli are numerous . . . . A. P.

80. From a culture of the pseudo-diphtheria bacillus of a case of human diphtheria . . . . A. P.

81. From a culture of a different kind of pseudo-diphtheria bacillus obtained from the milk of a cow. All bacilli are club-shaped or dumb-bell-shaped . . . . E. C. B.

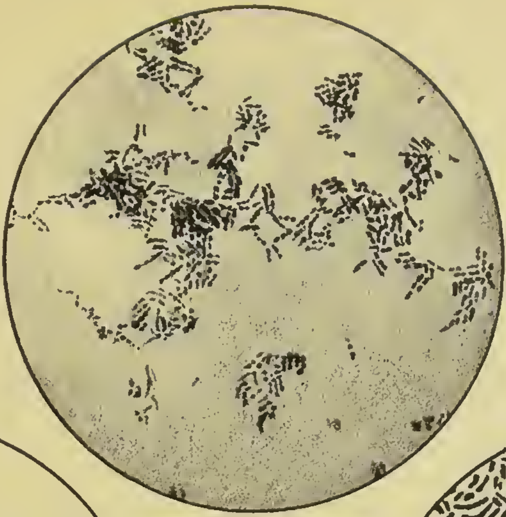
82. From a section through the necrotic part of the local tumour produced in the cow by subcutaneous inoculation of the human diphtheria bacillus. The dark masses are masses of the diphtheria bacillus located in a reticulated necrotic tissue. Low power . . A. P.

83. From a section through a pneumonic patch of the lung of cat dead of natural diphtheria. The infundibula and air cells are filled with necrotic masses in which nuclei of leucocytes are still to be recognised. Low power . . . . A. P.

84. From a section through the lower part of the larynx of a cat dead of diphtheria, contracted naturally by ingestion of the milk of an infected cow: on the left is the cartilage, on the right the necrotic mucosa which formed a complete grey false membrane in the larynx and upper part of the trachea. Low power . . . . . A. P.

Pl. XII.

78



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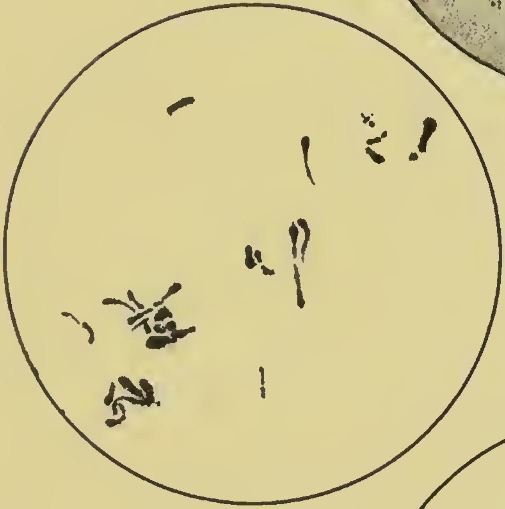

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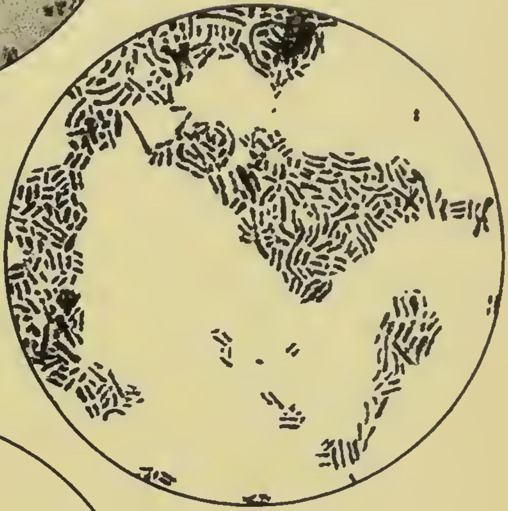

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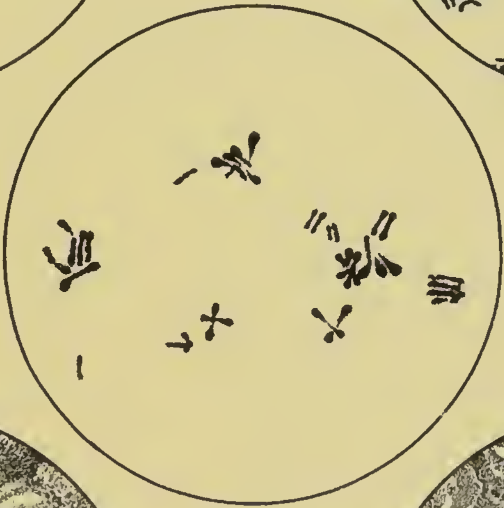

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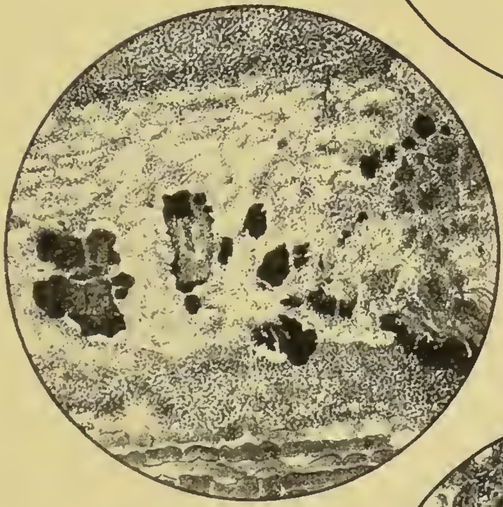

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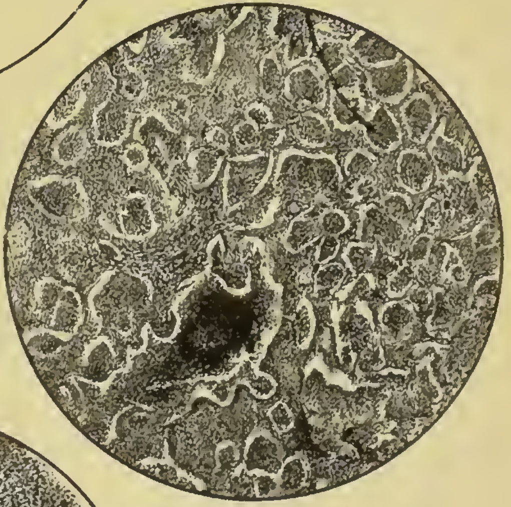

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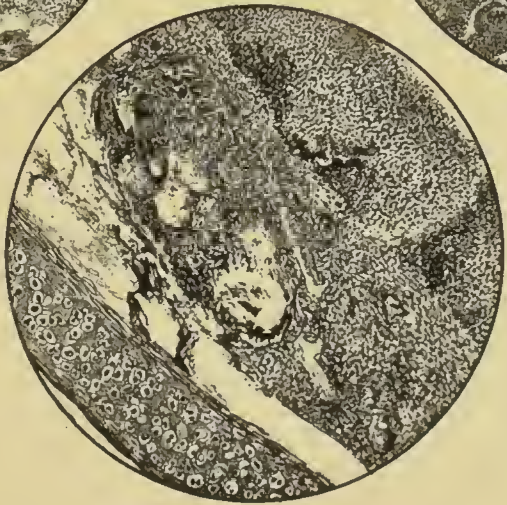


West, Newman lith.

PLATE XIII

FIG.

85. Cultivation on gelatine of the typhoid bacillus . . . . A. P.

86. Blood in relapsing fever, showing the spirilla of Obermeyer, copied from Koch.

87. From mucus flakes of the ileum of a case of cholera asiatica, showing the comma bacilli of Koch in almost pure culture. Magnifying power, 1,000 . . . . A. P.

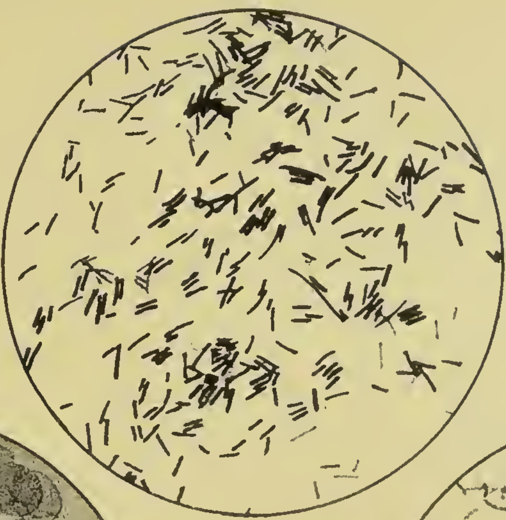
88. Mucus flakes of a case of Asiatic cholera. The comma bacilli in this case are several times the size of those shown in previous figure. One spirillum is here shown. Magnifying power, 1,000 . . . A. P.

89. Culture in gelatine of the choleraic comma bacilli . . . A. P.

90. Culture on agar of the choleraic comma bacilli; spirilla are shown . A. P.

91. Cultivation on gelatine of choleraic comma bacilli after several sub-cultures. The bacilli are very polymorphous, some quite spherical . . A. P.

85



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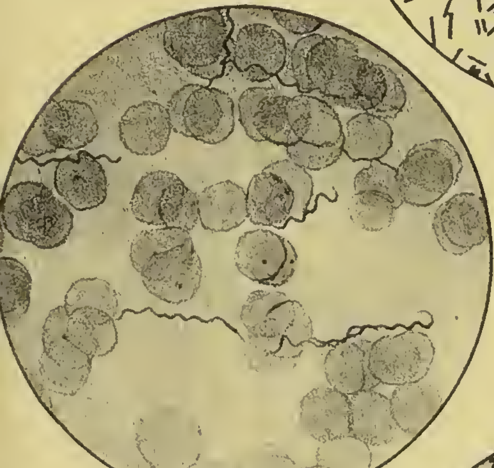

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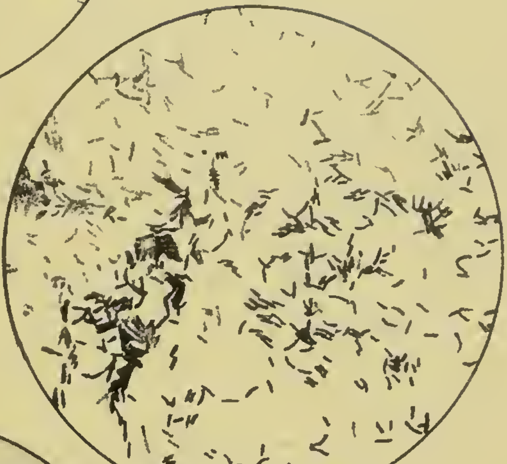

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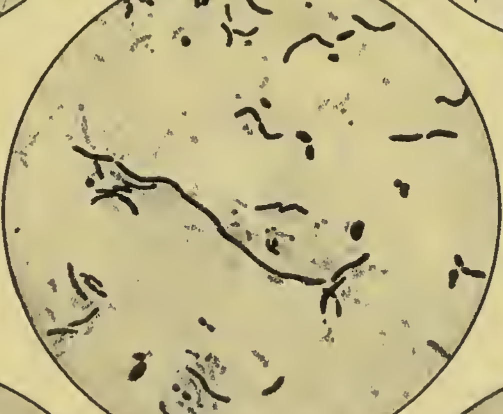

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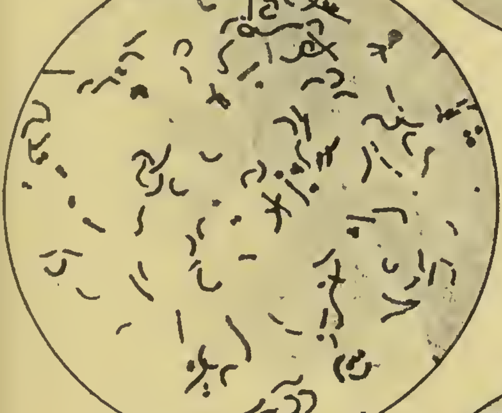

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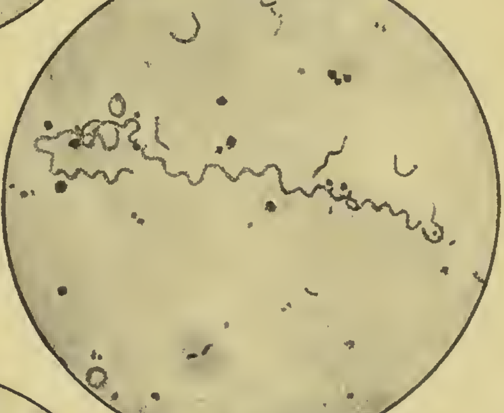

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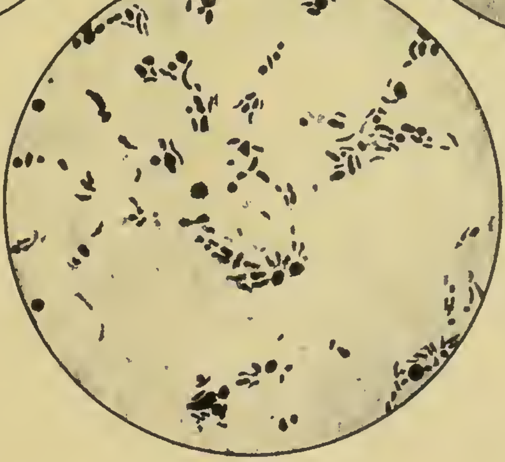


West, Newman lith.

PLATE XIV

FIG.

92. From a similar preparation as in fig. 91, but after more prolonged sub-cultures. The organisms are scarcely to be recognised as being related to the comma bacilli; some are much swollen up and full of vacuoles . . . . A. P.

93. Mucus flakes of an ape dead with symptoms of diarrhœa; comma bacilli in almost pure culture . . . . A. P.

94. Mucus from a loop of the intestine of an ape, after ligaturing the loop and injecting into its cavity sulphate of soda solution. Numerous minute comma bacilli and spirilla are seen . . . . A. P.

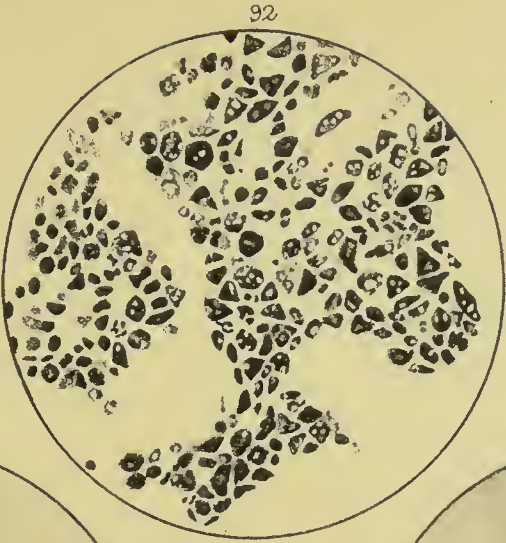
95. Blood of a case of influenza. Numerous minute bacilli seen amongst the blood discs . . . . E. C. B.

96. Specimen of pus of gonorrhœa. Two pus corpuscles are shown which contain in their interior numerous gonococci . . . E. C. B.

97. Pus of catarrhal ophthalmia or Egyptian ophthalmia (Koch). Numerous minute bacilli are seen free and within the substance of the pus corpuscles . . . . E. C. B.

98. From the same specimen as fig. 97. A large epithelial scale is shown, the surface of which is covered with the small bacilli . E. C. B.

92



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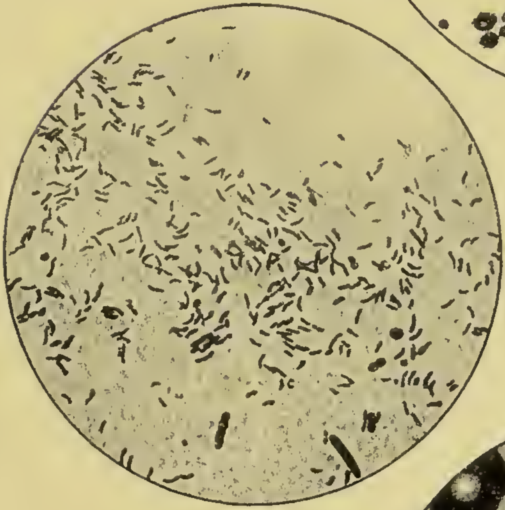

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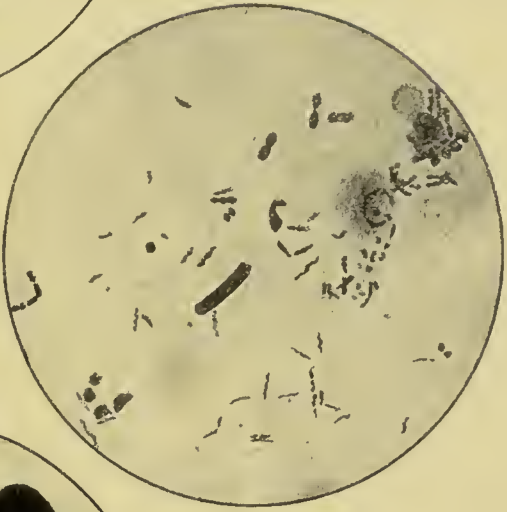

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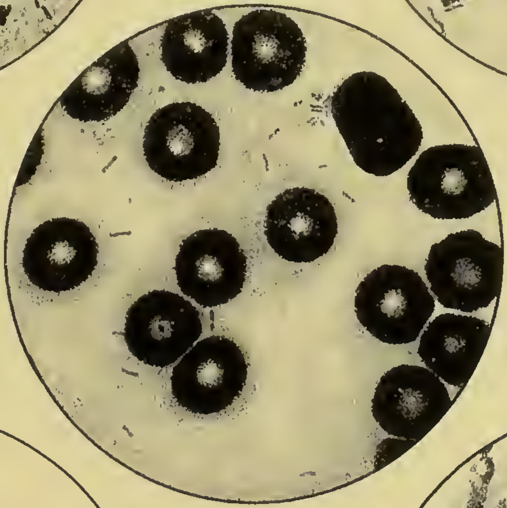

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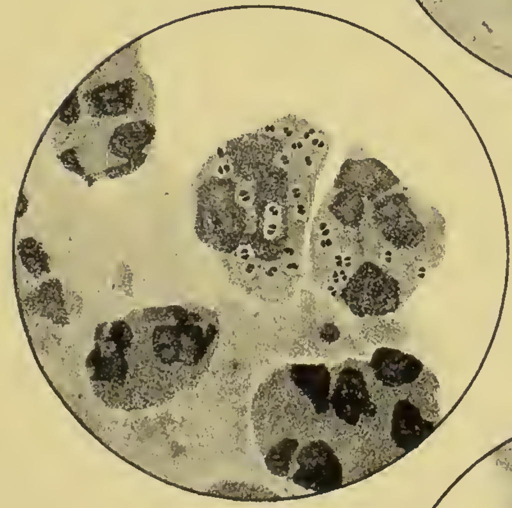

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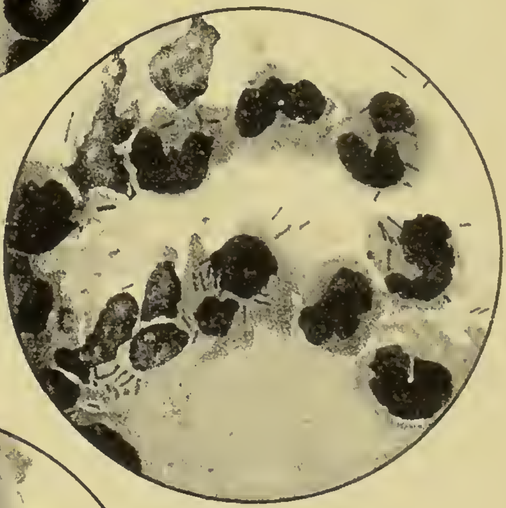

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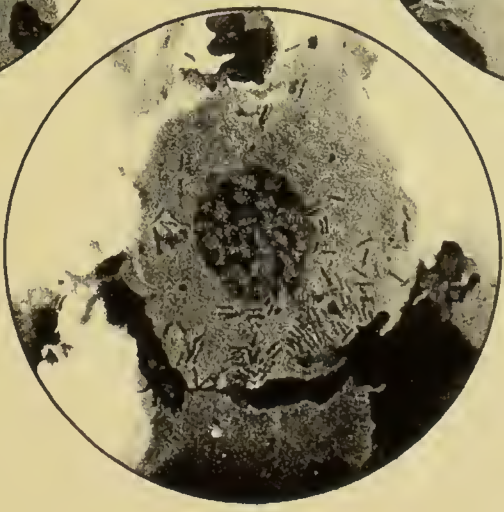

Wm Newman lith

PLATE XV

FIG.

99. Culture of minute bacilli, isolated from a beef pie that had caused choleraic diarrhœa at Portsmouth . . . . . . E. C. B.

100. Cover-glass specimen of lung juice of a nodule of the lung in glanders of the horse. The bacilli of glanders are shown very numerously. A. P.

101. Cultivation on agar of the glanders bacillus . . . . . A. P.

102. Cultivation of the tetanus bacillus. Some of the bacilli show the spore formation at one pole. These bacilli look like drumsticks . . A. P.

103. Cover-glass specimen of pulmonary sputum in tuberculosis. The tubercle bacilli are very numerously present, few nuclei of pus cells . A. P.

104. From a culture on glycerine agar of the tubercle bacilli . . A. P.

105. Purulent matter of a human cerebral abscess, due to tubercle. Two leucocytes are shown, containing the tubercle bacilli . . A. P.

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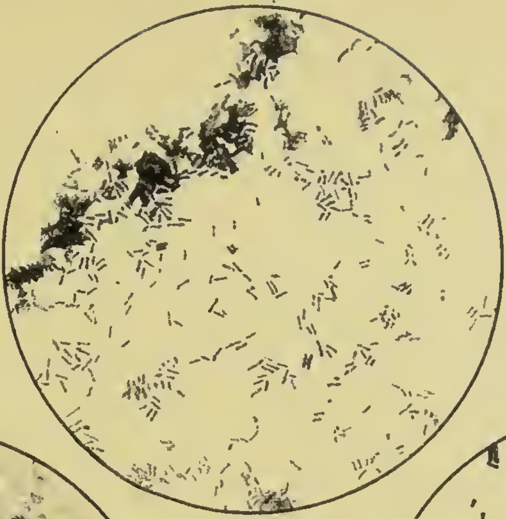
Pl. XV.

(Klein.)

99.



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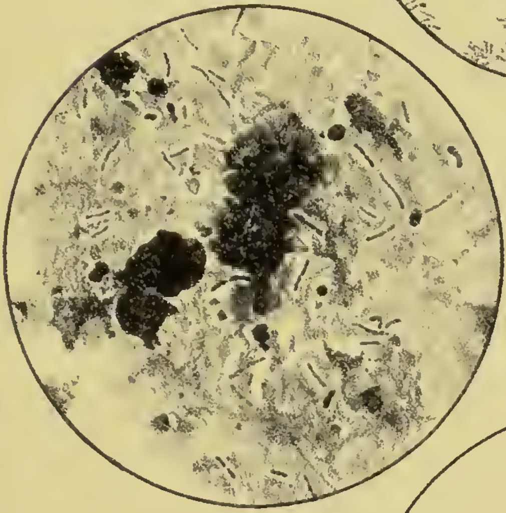

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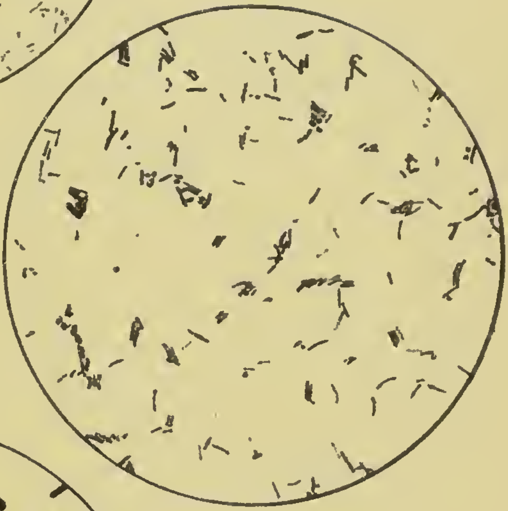

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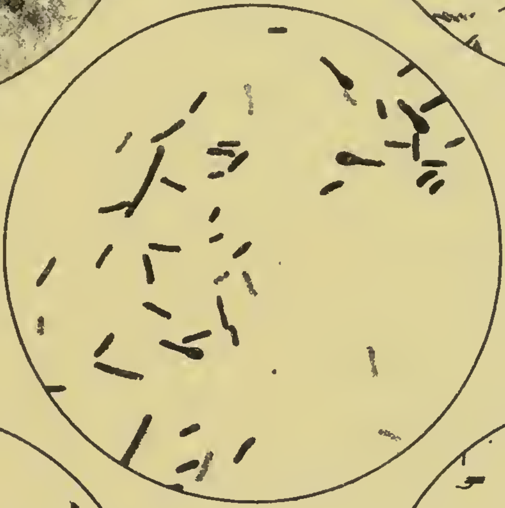

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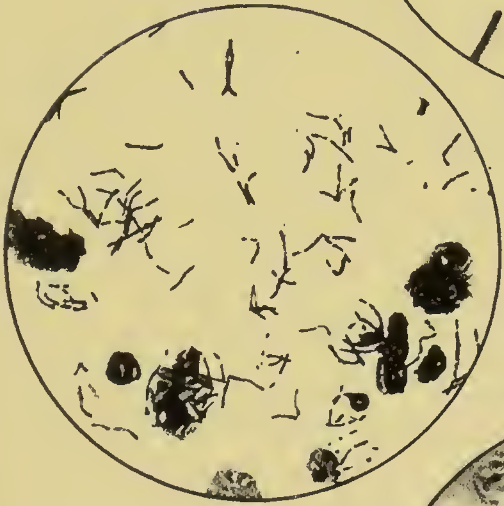

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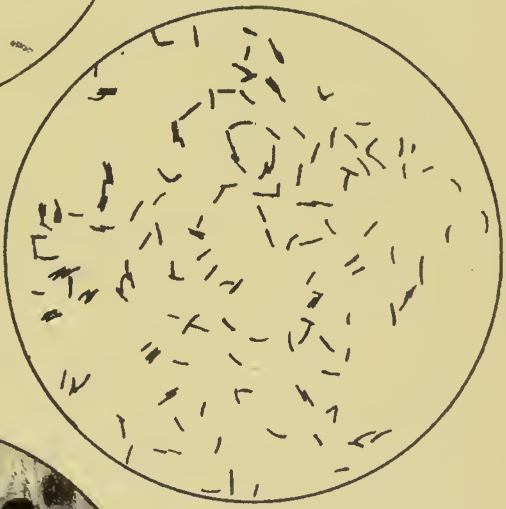

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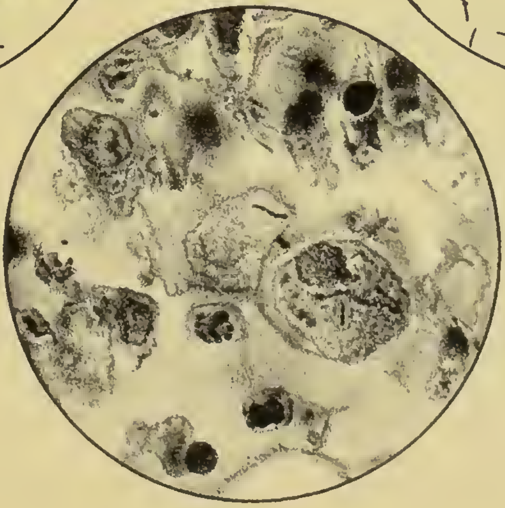


West, Newman lith.

PLATE XVI

FIG.

106. Section through a tubercle of the human lung. Low power . A. P.

107. The centre of a caseous tubercle in the human lung (same specimen as shown in previous figure), numerous tubercle bacilli in the central part. Magnifying power, 650 . . . . A. P.

108. From a section through a pulmonary tubercle in the cow ; a giant cell full of tubercle bacilli, also other isolated tubercle bacilli . . A. P.

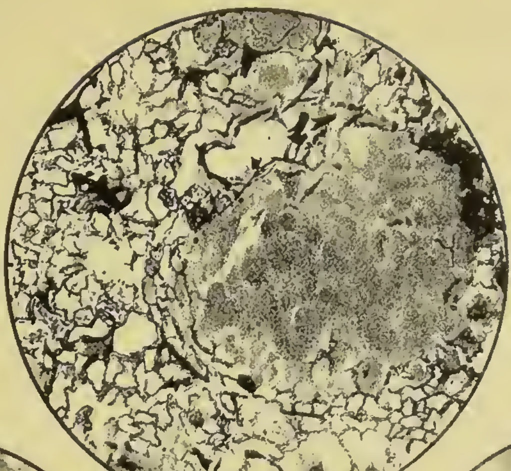
109. A grey tubercle in the lung of a rabbit developed in a few weeks after injection of culture of tubercle bacilli into the vein of the ear. The centre of the tubercle is surrounded by leucocytes containing the tubercle bacilli . . . . A. P.

110. From a tubercle in the liver of a rabbit infected by intravenous injection of culture of tubercle bacilli. Two giant cells full of tubercle bacilli are shown . . . . E. C. B.

111. From a section through caseous tubercle of the spleen of a fowl. Groups of tubercle bacilli in the necrotic tissue . . . A. P.

112. One large giant cell of a tubercle in the lung of a cow. Numerous tubercle bacilli are shown in the substance of the giant cell . A. P.

106



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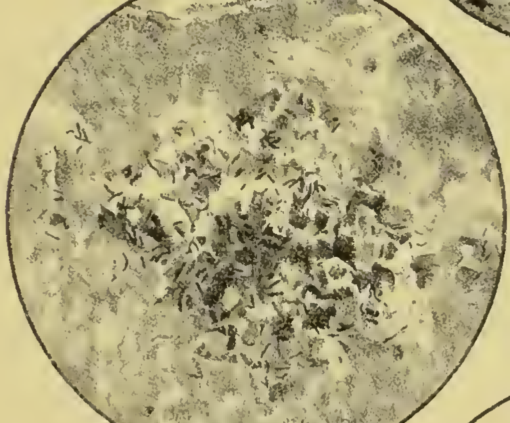

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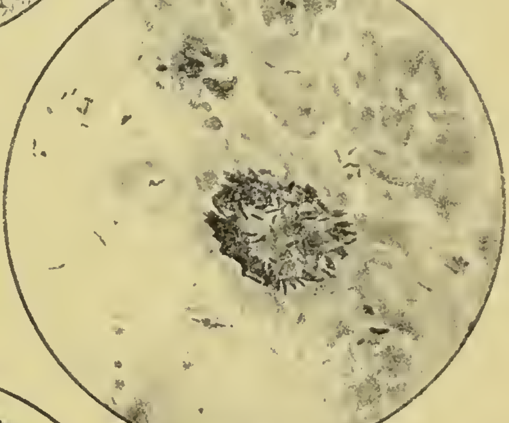

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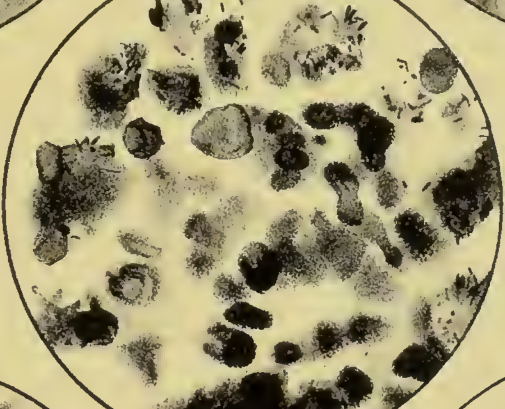

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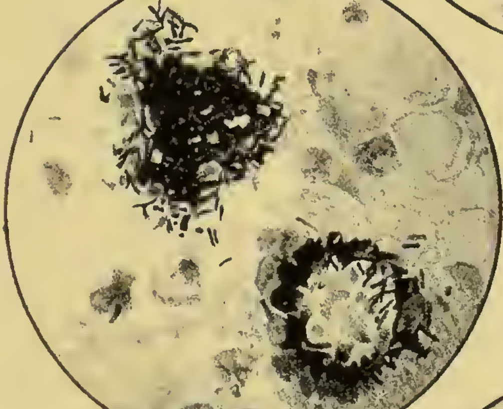

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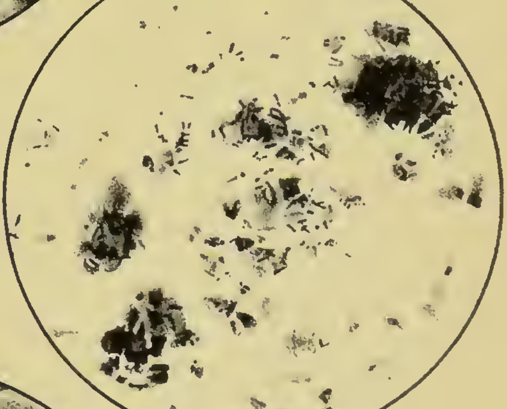

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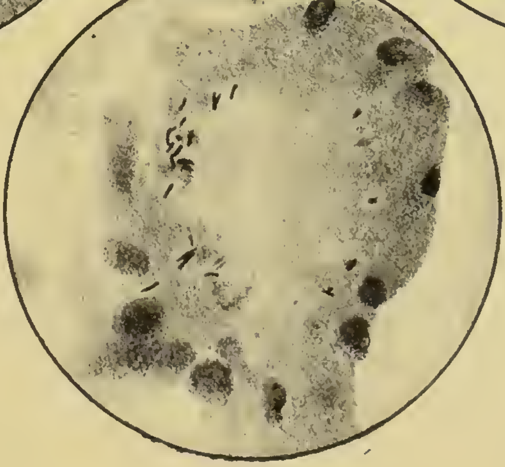


West Newman lith.

PLATE XVII

FIG.

113. Large cells of a leprous nodule, containing an abundance of the lepra bacilli, free and particularly filling the substance of the cells . A. P.

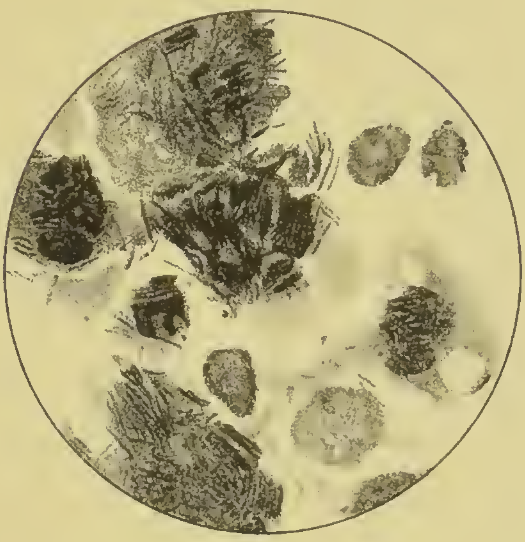
114. A similar preparation as in previous figure . . . . . A. P.

115. Section through the tongue of ox. Numerous round-cell nodules, the centre of which is occupied by a mass of actinomyces. Low power. A. P.

116. From a similar preparation, more highly magnified, showing the actinomyces mass. The 'rays' are distinct . . . . . A. P.

117. A similar preparation, highly magnified; the 'clubs' of the rays are well shown . . . . A. P.

118. Part of the mycelium of actinomyces, from a culture on gelatine of the actinomyces. Branched threads are shown, which threads are either homogeneous, or they show granules, or they are made up of rods and cylinders . . . . E. C. B.



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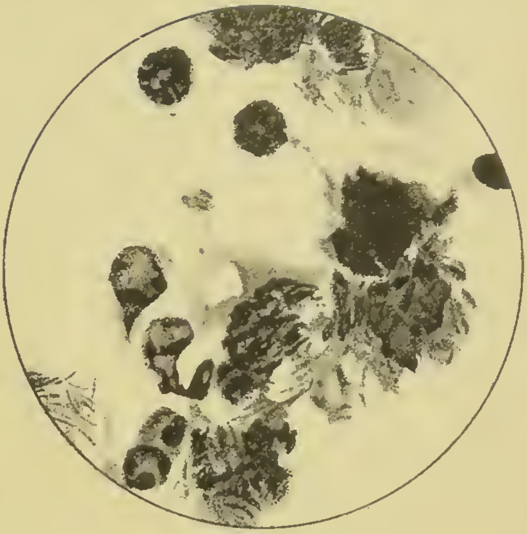

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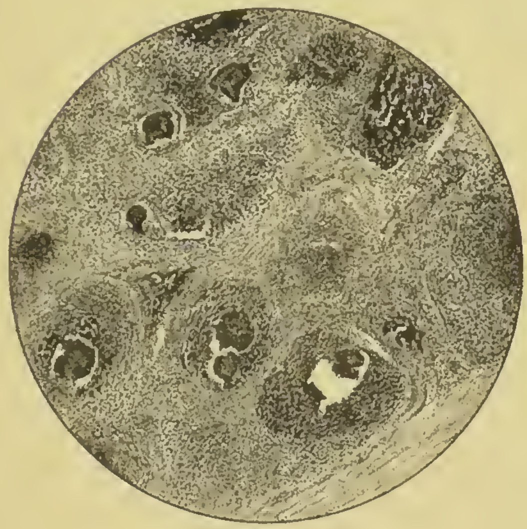

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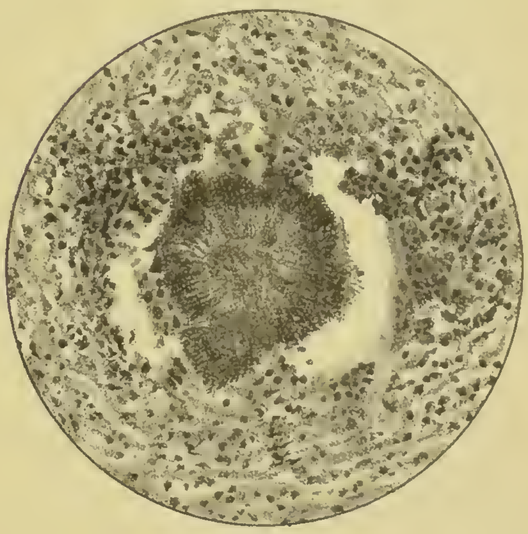

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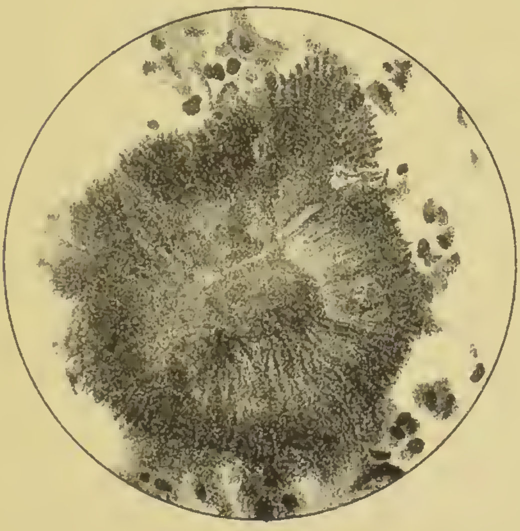

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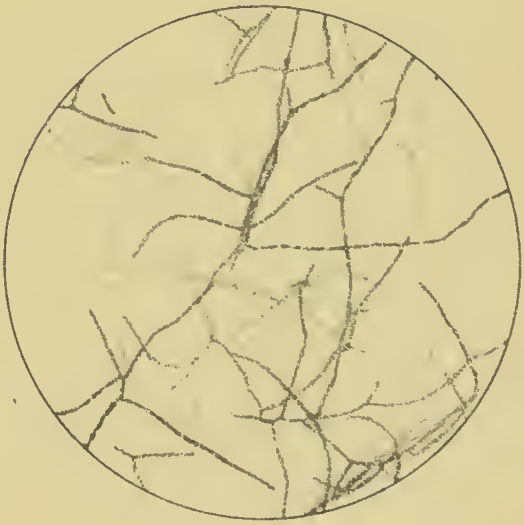

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West, Newman lith.

Plates XVIII–XXV inclusive (figures 119 to 152) are from drawings made by Mr. M. H. Lapidge.

PLATE XVIII

Fig.

119. Bacillus filamentosus with spores. The bacillary threads are stained in methyl blue, the spores in fuchsin. Magnifying power, 750.

120. Bacillus anthracis from a potato culture. The bacilli are stained in methyl blue, the spores in fuchsin. Magnifying power, 350.

121. Pus from gonorrhœal discharge, showing pus cells, some containing in their interior the gonococci stained with gentian violet. Magnifying power, 700.

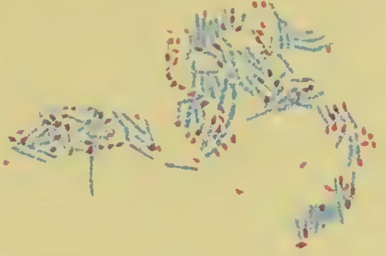
122. Two pus cells of gonorrhœal discharge, containing numerously the gonococci as diplococci. Same specimen as fig. 121. Magnifying power, 1,400.

123. Purulent conjunctival discharge of true Egyptian ophthalmia of Koch. Pus cells indicated by their nuclei, containing at *a* fine bacilli; at *b* masses of free bacilli. Methyl blue staining. Magnifying power, about 1,000.

124. Section through the valve in ulcerative endocarditis. The section was stained in methyl blue. The blue masses are masses of streptococci. Magnifying power, 100.

125. Section through the valve in another case of ulcerative endocarditis, stained with methyl blue and eosin. The blue masses are masses of staphylococcus aureus; *a* is the free edge of the villous valve. Magnifying power, 100.

120



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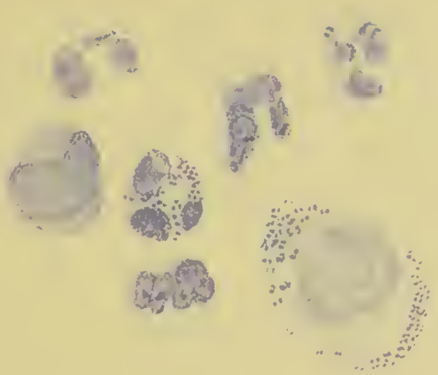

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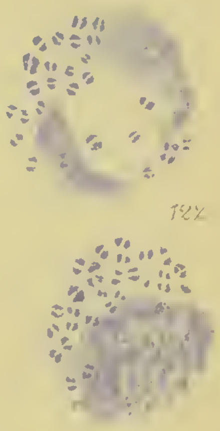

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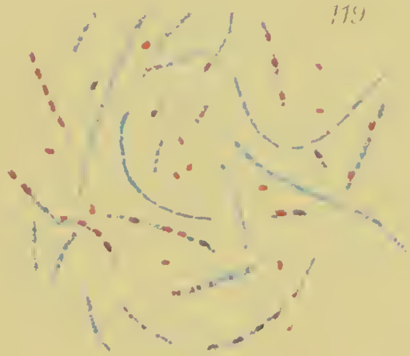

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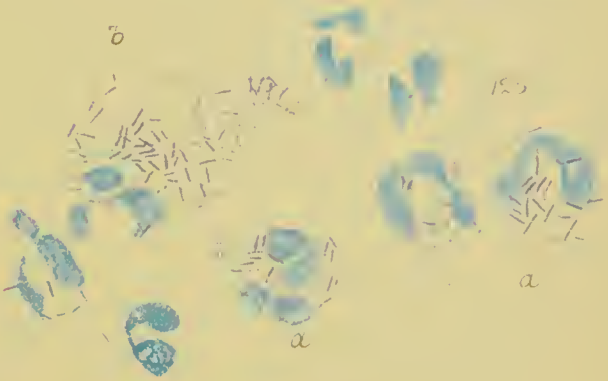

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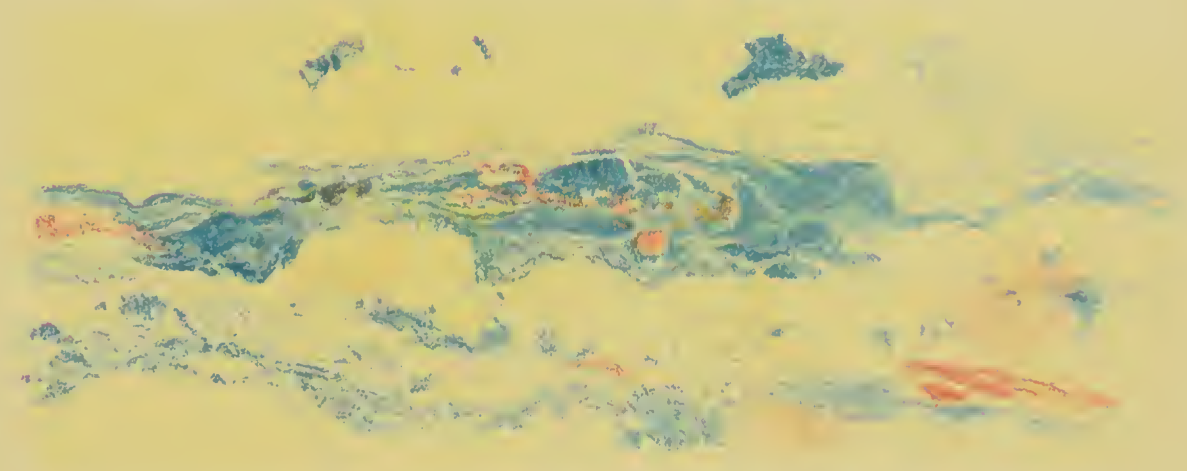

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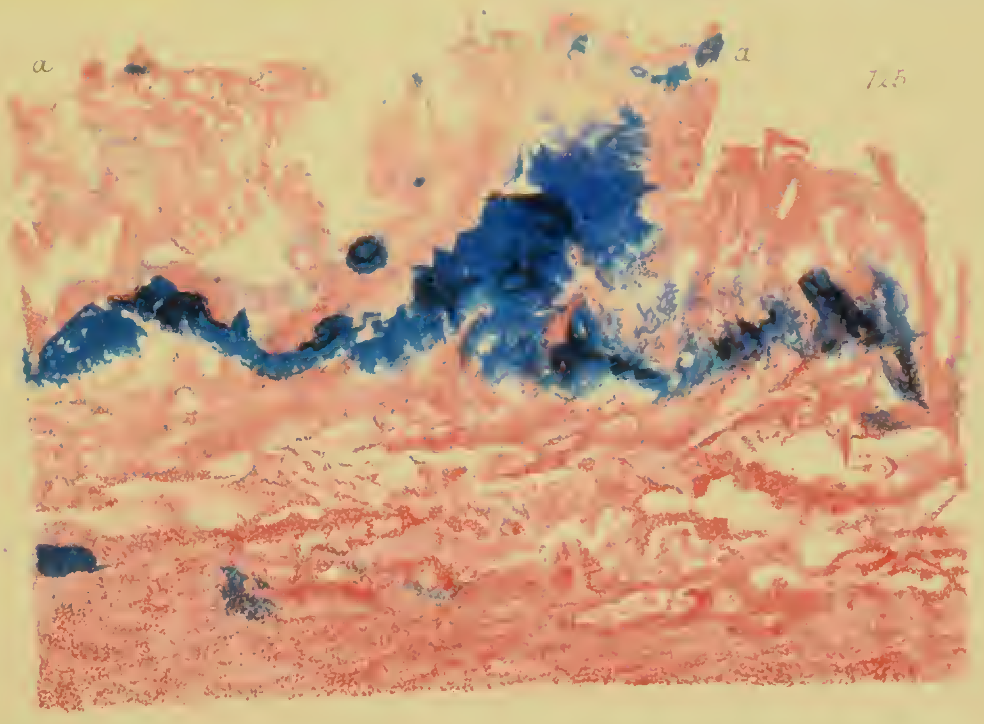

West, Newman ch

PLATE XIX[1]

FIG.

126. From a section through the medulla of the kidney of a rabbit after injection into the ear vein of a culture of the staphylococcus aureus of the above case of ulcerative endocarditis, stained in methyl blue and eosin. The blue masses are masses of staphylococcus aureus filling blood-vessels ; the red ground are uriniferous tubules. Magnifying power, 100.

Figs. 124, 125, and 126 are from preparations by Dr. F. H. Andrewes.

133. From a section through the mucous membrane of the pharnyx of a child dead of acute diphtheria, stained in gentian violet : (*a*) surface of the false membrane filled with the diphtheria bacilli ; (*b*) the mucous membrane filled with extravasated blood. Magnifying power, about 300.

137. The kidney of a cat that died after ten to twelve days' illness of diphtheria naturally acquired. The enlargement and fatty white cortex are conspicuous. Natural size.

138. The kidney of a cat that died after five to six days' illness, resulting from inoculation of the diphtheria bacilli. Natural size.

133, 137, and 138 are copied from Klein's ' Etiology of Diphtheria ' in the Reports of the Medical Officer of the Local Government Board for 1889.

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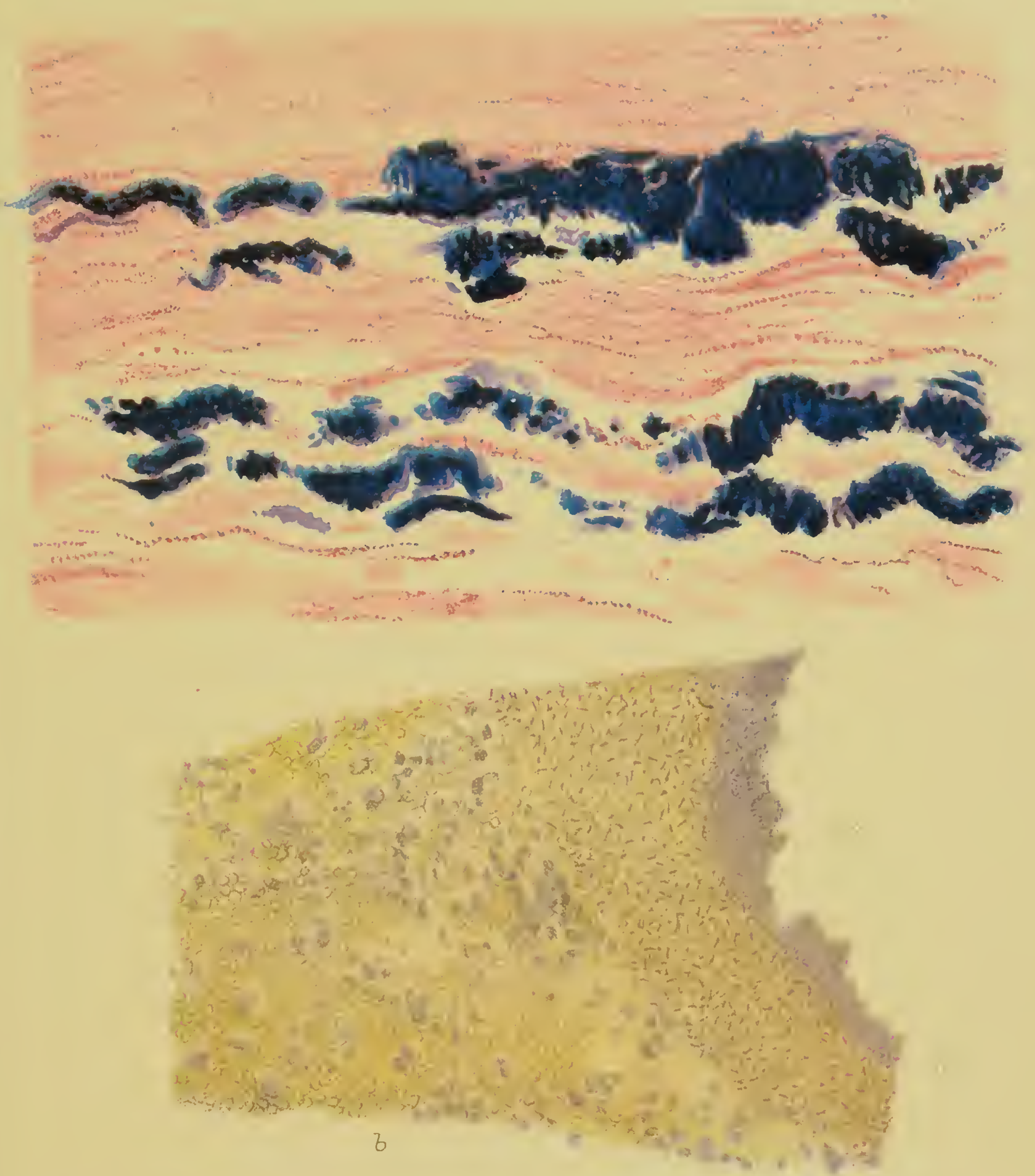
[1] The making up of this and some of the subsequent plates necessitated a slight derangement in the numbers of the figures.

136



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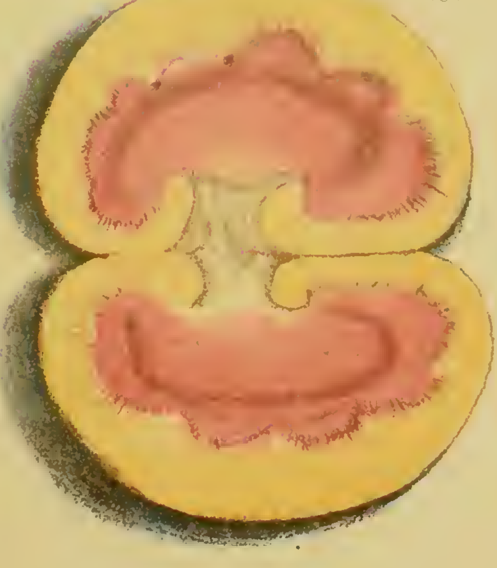

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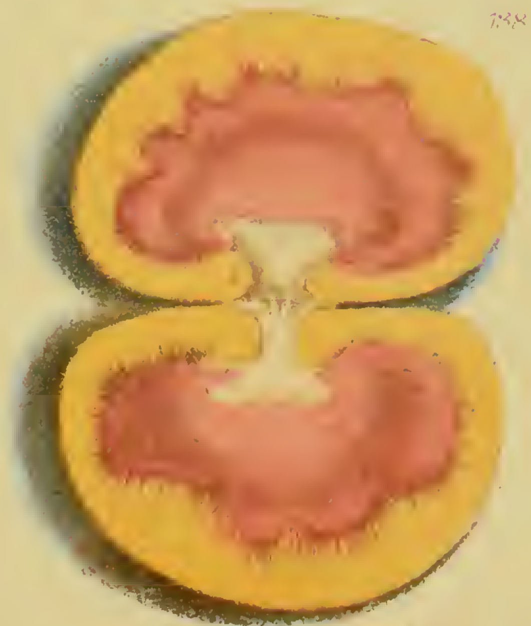


W. Newman chr.lith

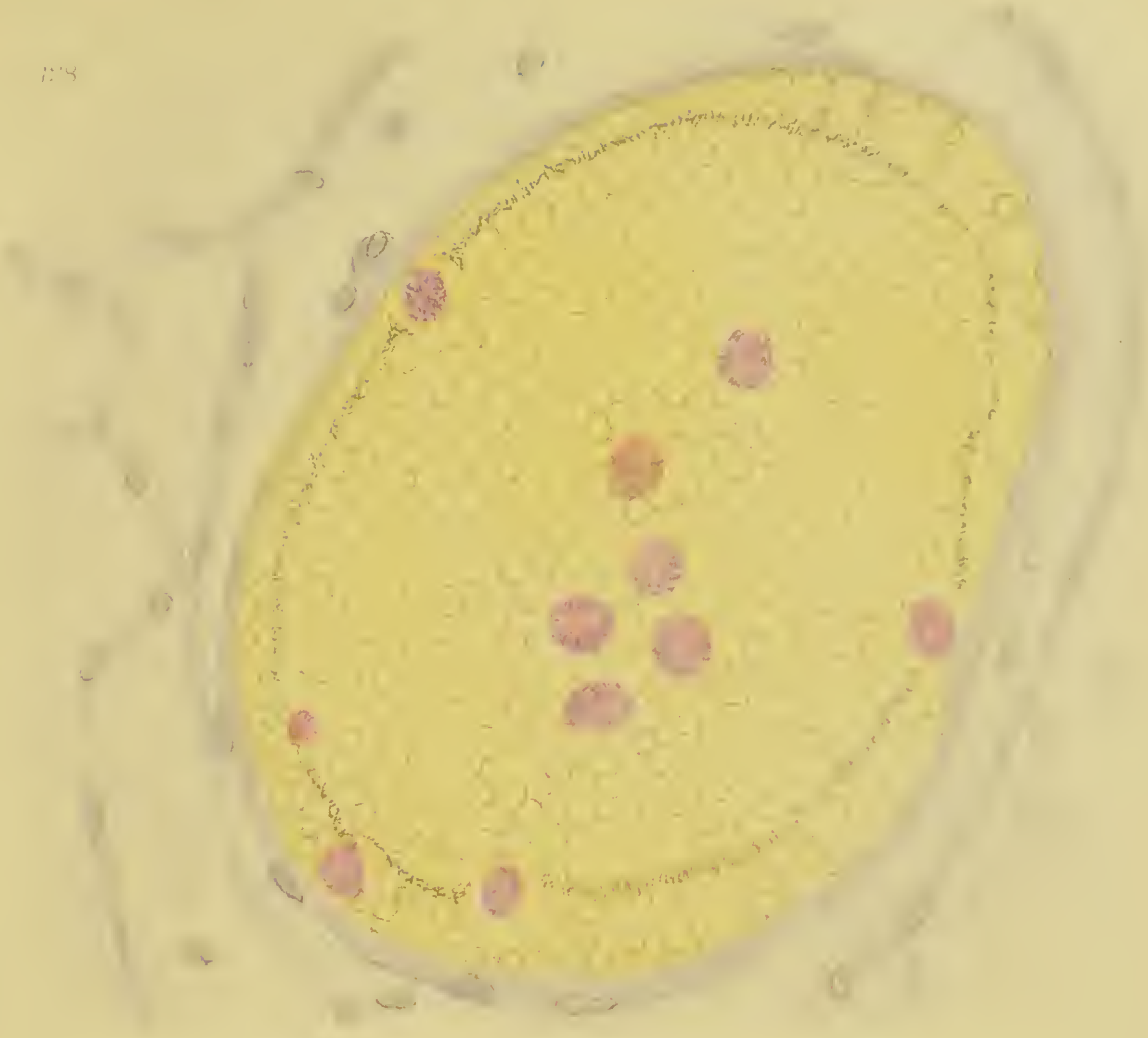
PLATE XX

Fig.

128. From a section through the lung of a mouse dead of Koch's acute mouse septicæmia. Stained with gentian violet. A large blood-vessel is here represented, distended by and filled with blood, the white blood cells containing in their cell substance numerously the fine bacilli. M. P. 700.

131. Section through the cortex of the kidney of a rabbit dead of virulent anthrax, stained with Spiller's purple: (*a*) Malpighian corpuscles, the capillaries of which are distended by and filled with the bacilli anthracis; (*b*) capillary blood-vessels filled with the bacilli. M. P. about 300.

128



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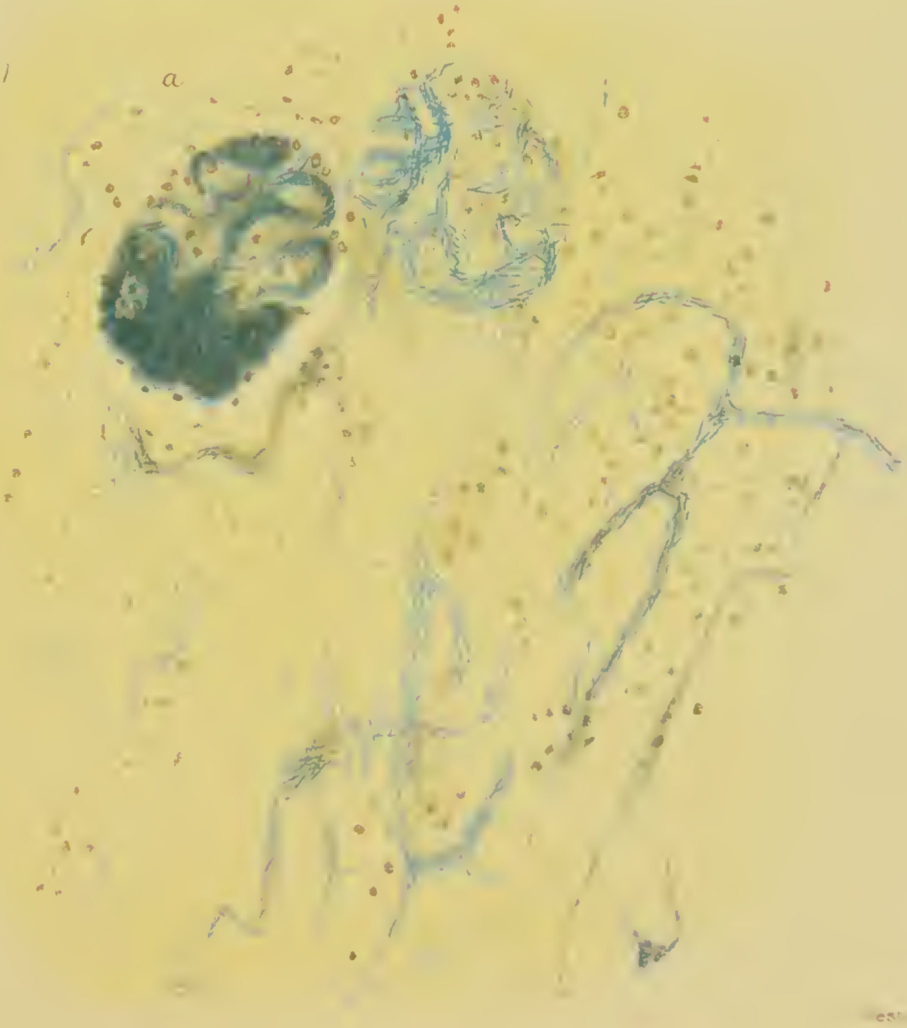


[illegible]

PLATE XXI

FIG.

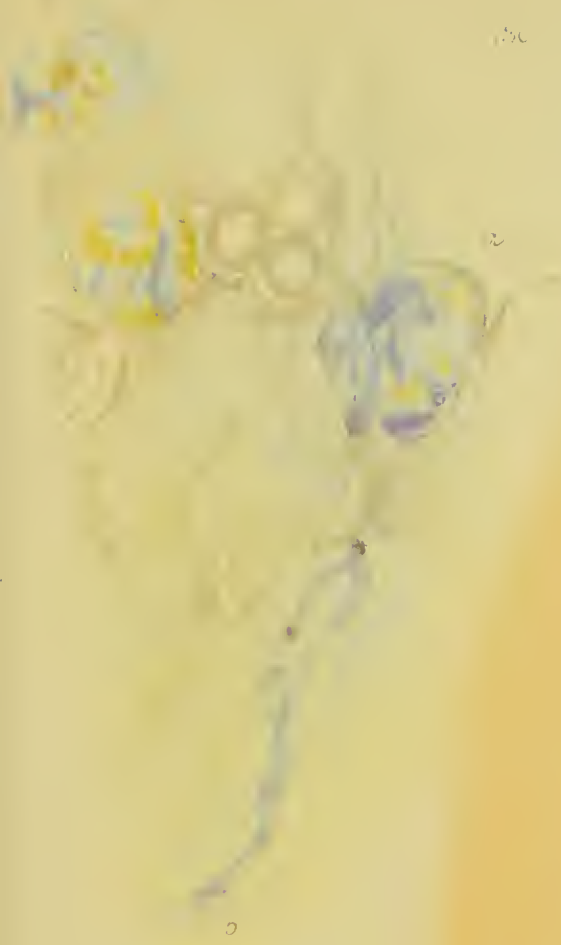
130. From a section through the kidney of a mouse dead after inoculation with culture of the bacillus of swine fever, stained with methyl blue: (*a*) A Malpighian corpuscle, its capillary blood-vessels filled with the bacilli; (*b*) capillary blood-vessels filled with the bacilli. M. P. 175.

136. The eruption on the sixth day on the udder of a cow subcutaneously inoculated into the shoulder with a culture of the bacillus diphtheriæ: (*a*) The teats; (*b*) the eruption: some are still in the stage of vesicles, others are already covered with black crusts. Natural size.

129. From a section through the lung tissue of a mouse dead of Koch's acute mouse septicæmia. In the tissue separating the lung alveoli leucocytes are seen, whose protoplasm includes numerously the characteristic minute bacilli, stained with gentian violet. M. P. about 1000.

127. Section through a necrotic patch in the liver of a mouse dead after septicæmia: (*a*) Capillary blood-vessels distended, and containing besides blood-corpuscles masses of minute bacilli stained blue; (*b*) the strands of necrotic liver cells. The section had been stained in methyl blue and eosin. M. P. about 300.

35



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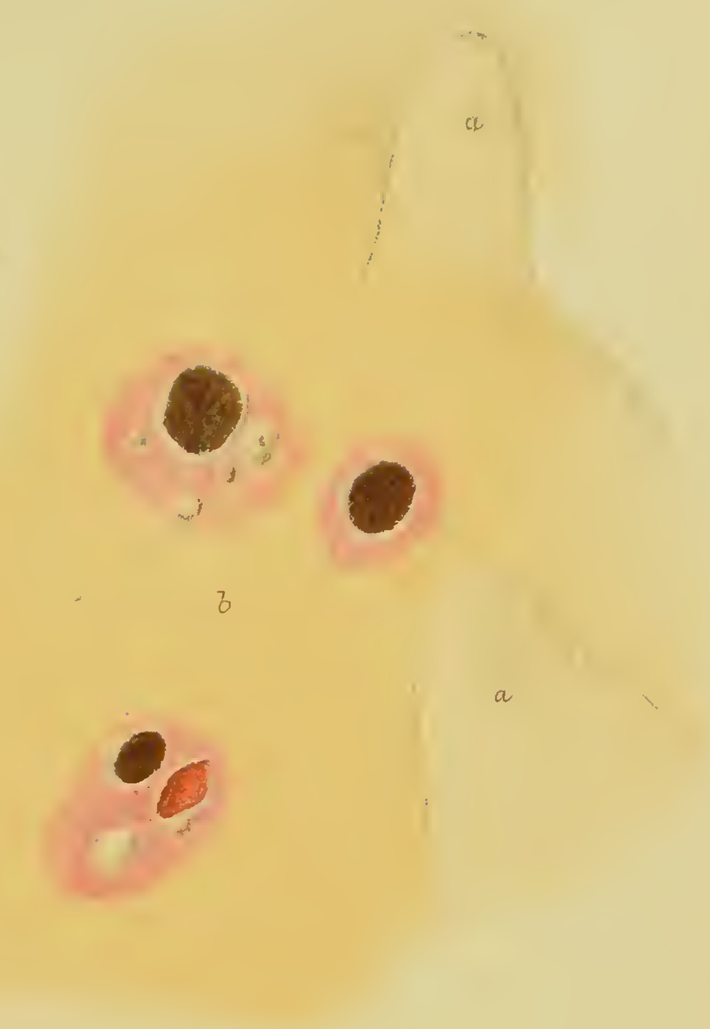

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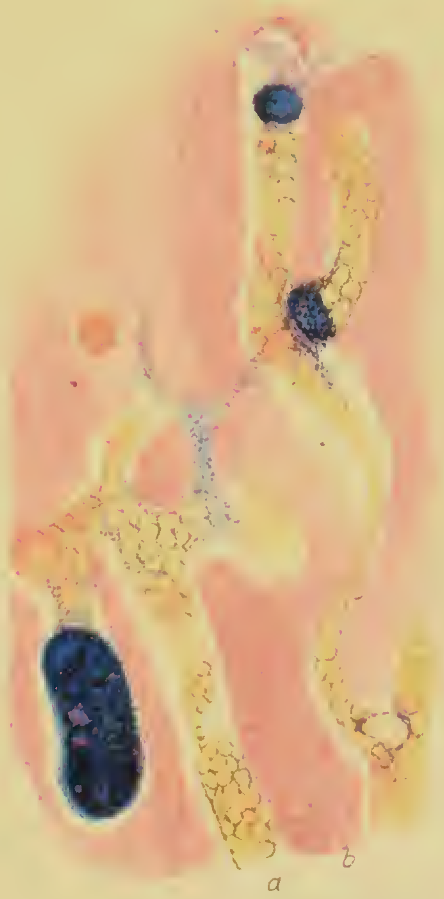


West, Newman chr. lith.

PLATE XXII

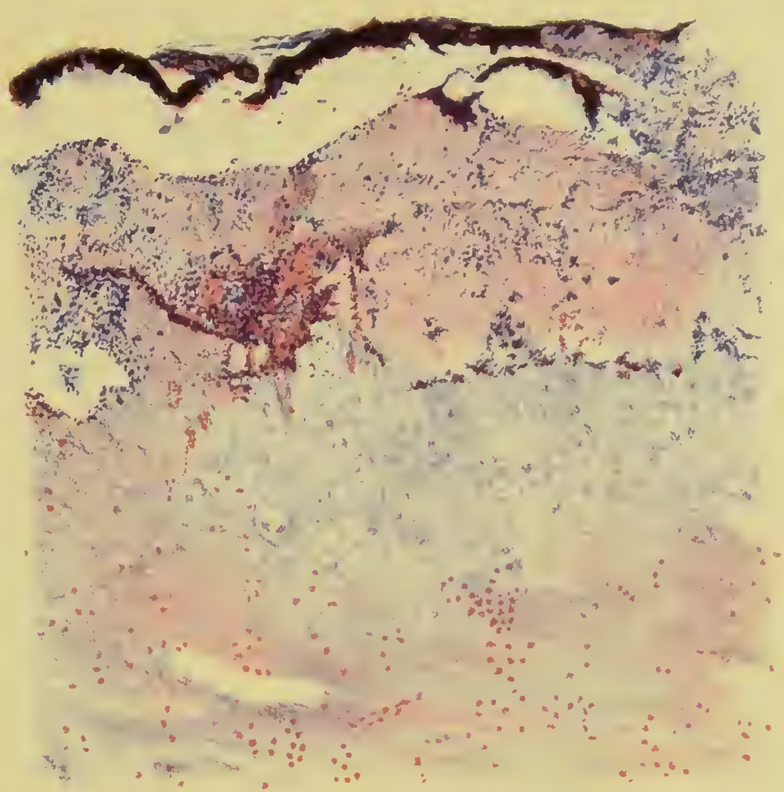
FIG.

132. From a section through the mucous membrane of the larynx of a child dead of diphtheritic croup. The mucous membrane is transformed into a typical diphtheritic membrane, in the superficial layers of which are large numbers of the diphtheria bacilli, stained blue. On the free surface of the membrane they form an almost continuous mass. The section was stained in rubin and then in methyl blue. M. P. 100.

135. Cover-glass specimen of the superficial parts of the diphtheritic membrane, showing cells and numerous diphtheria bacilli, stained blue, free and enclosed within the cells. The preparation was stained in rubin and then in methyl blue. M. P. about 700.

134. Section through the diphtheritic membrane from the tonsil of a child. The section shows in the superficial layers of the membrane (lower part of figure) almost continuous loculi, large and small, filled with clumps of the diphtheria bacilli, stained blue; in the middle portions are also numerous smaller masses of the bacilli. The section had been stained with rubin and then with methyl blue. M. P. about 100.

139. From a section through a necrotic nodule of the lung in a horse dead of glanders. Numerous bacilli of glanders, stained blue, are seen. The section had been stained in rubin and then in methyl blue. M. P. about 1,000.



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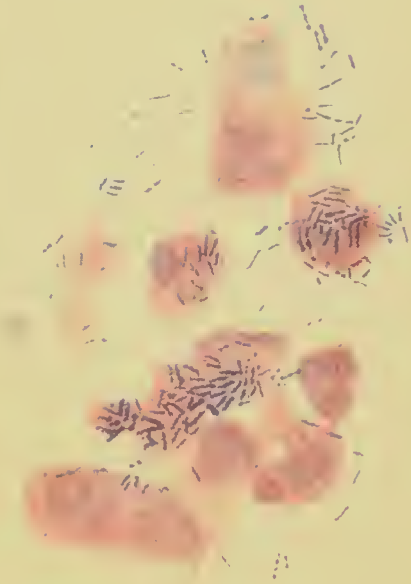

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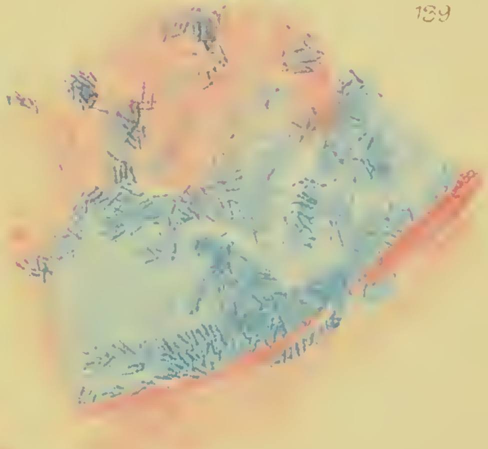

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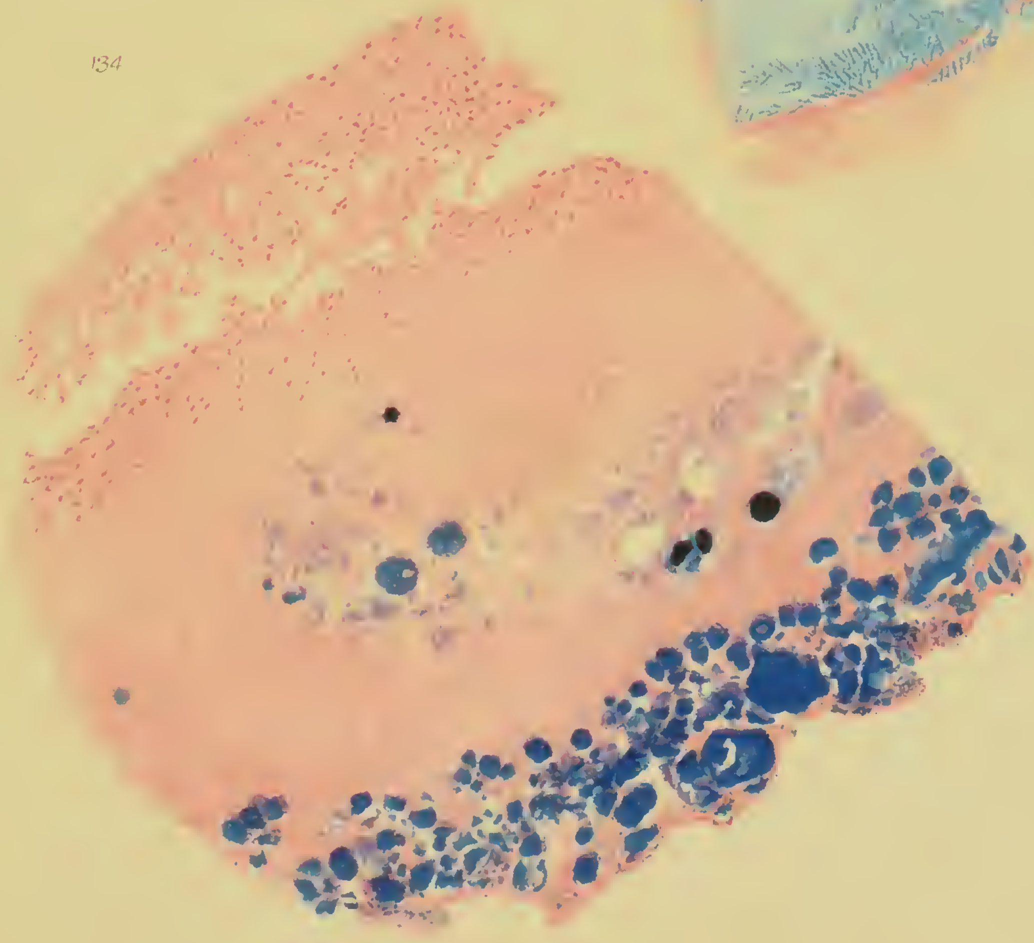


West, Newman chr

PLATE XXIII

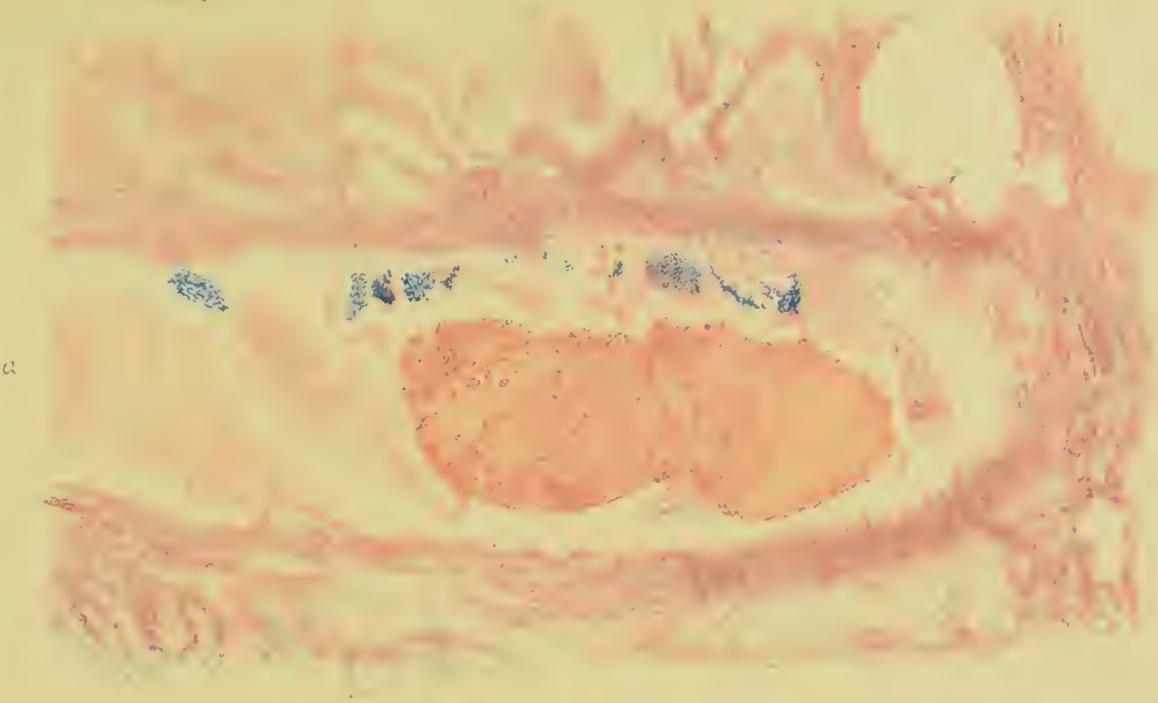
Fig.

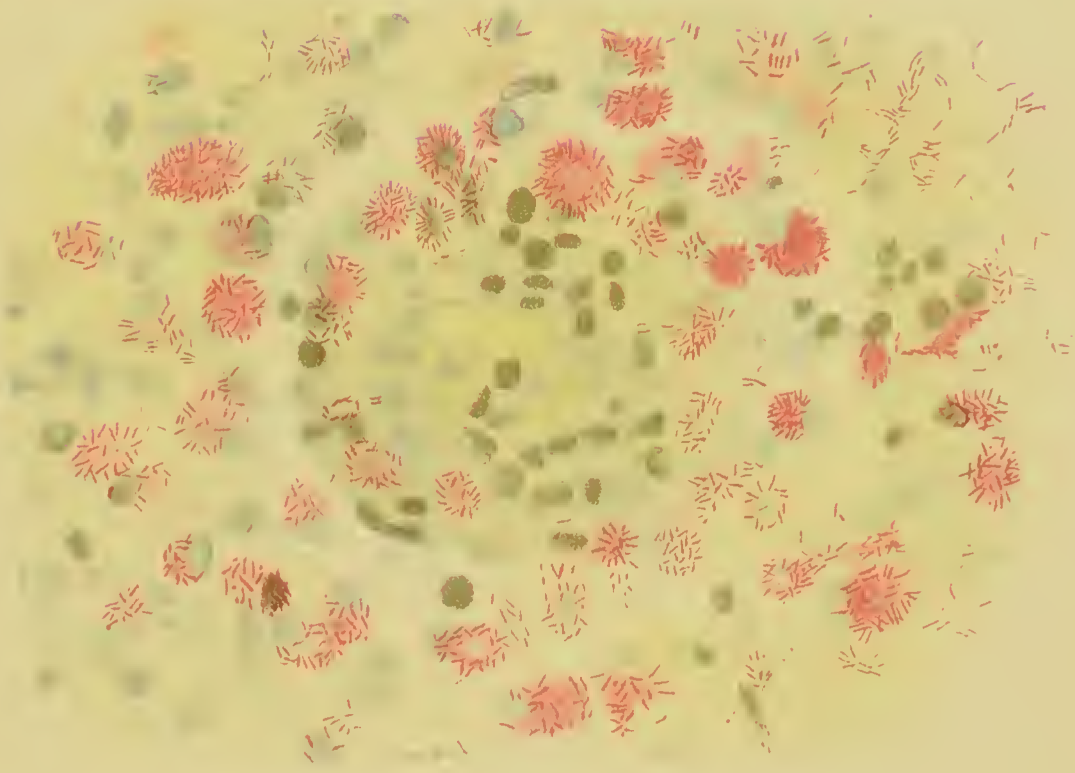
140. From a section through the glanders lung of horse. The section represents a large lymphatic vessel containing a coagulum. In the upper part of the contents of the vessel are several blue clumps of the glanders bacilli ; stained with rubin and then methyl blue. M. P. 100.

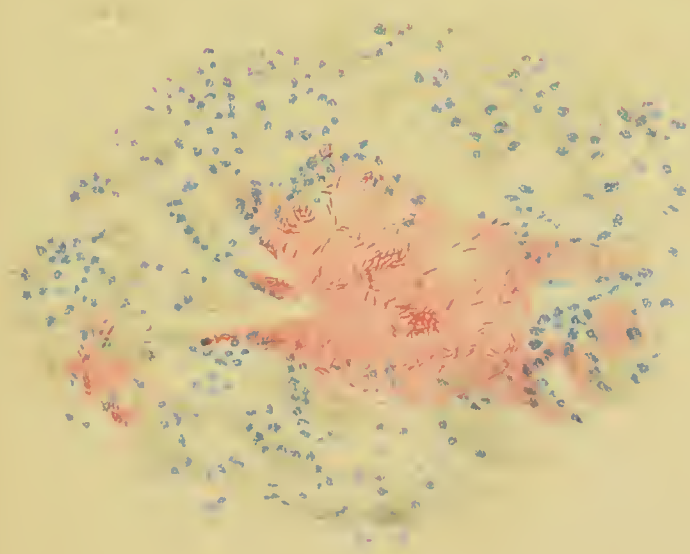
141. Section through a young tubercle in the lung of rabbit ; numbers of cells are seen filled with the tubercle bacilli—carbol fuchsin, nitric acid, and then methyl blue. M. P. about 1,000.

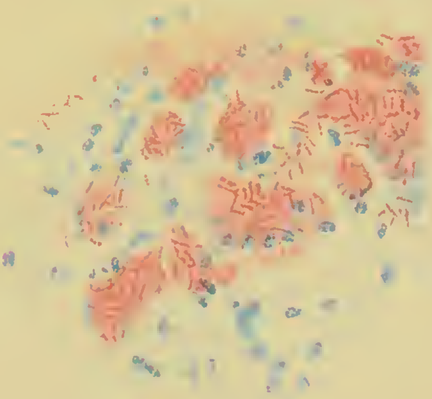
142. From a section through a tubercle in the spleen of a fowl artificially infected with human tubercle. The central part is a caseous mass containing abundantly the tubercle bacilli—carbol fuchsin, nitric acid, and then methyl blue. M. P. 300.

143. From a similar tubercle as in fig. 142, but more highly magnified. M. P. 1,000.









West, Newman chr. lith.

PLATE XXIV

FIG.

144. A giant cell in a tubercle in the lung of a cow—carbol fuchsin, nitric acid, and then methyl blue. The tubercle bacilli form a characteristic peripheral annular zone. Magnifying power, 1,000.

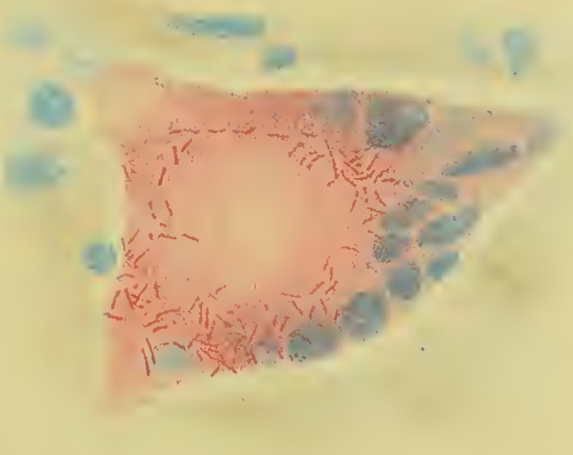
145. Section through a cutaneous leprous nodule—carbol fuchsin, nitric acid, and then methyl blue. (*a*) The stratum corneum of the epidermis; (*b*) the stratum Malpighii; (*c*) the superficial layer of the cutis; (*d*) the upper part of the leprous nodule. In this, numbers of lepra cells filled with the lepra bacilli. Also in the layers above there are a few lepra bacilli seen. Magnifying power, 300.

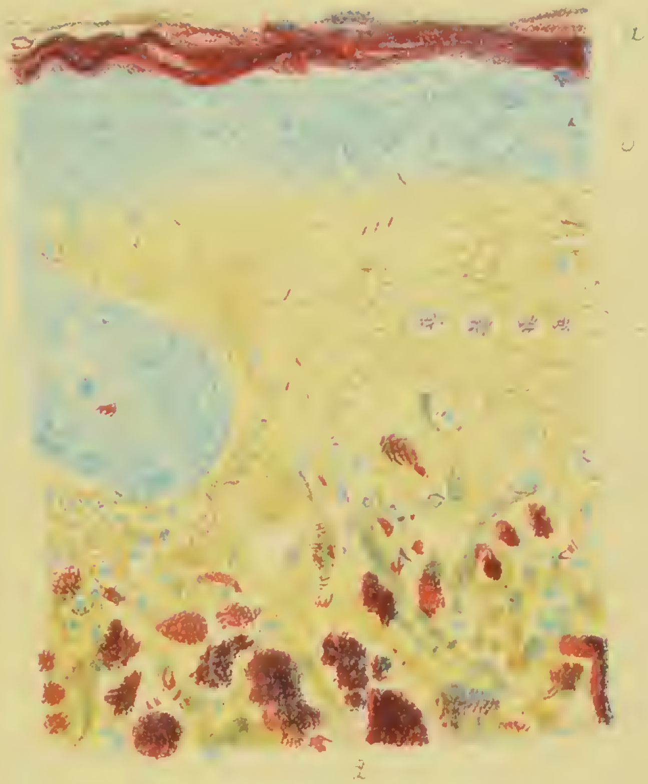
146. Section showing the middle part of a cutaneous leprosy nodule, same as in fig. 145. The tissue of the nodule contains cells of different sizes, the substance of all of them filled with the lepra bacilli. Magnifying power, 300.

147. Cover-glass specimen of the purulent secretion of an ulcerated leprosy nodule, showing the leprosy cells filled with bundles of the lepra bacilli. Magnifying power, 1,000.

148. From a section through the liver of a Rhea. The liver was crowded with white nodules. Such a nodule is here shown as composed of densely aggregated cells, each filled with extremely minute bacilli, stained red with fuchsin. Fuchsin and nitric acid. Magnifying power, 300.

149. Several of the cells of fig. 148 shown, more highly magnified. Magnifying power, 1,000.





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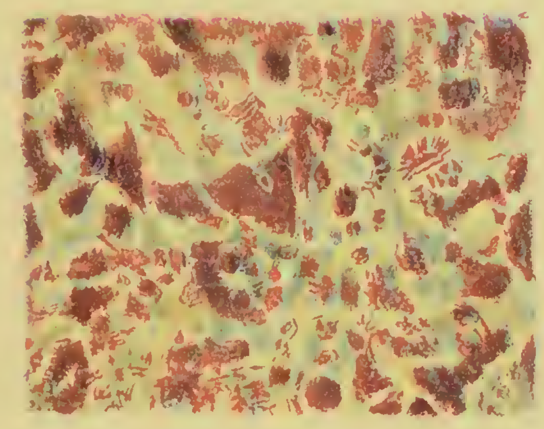

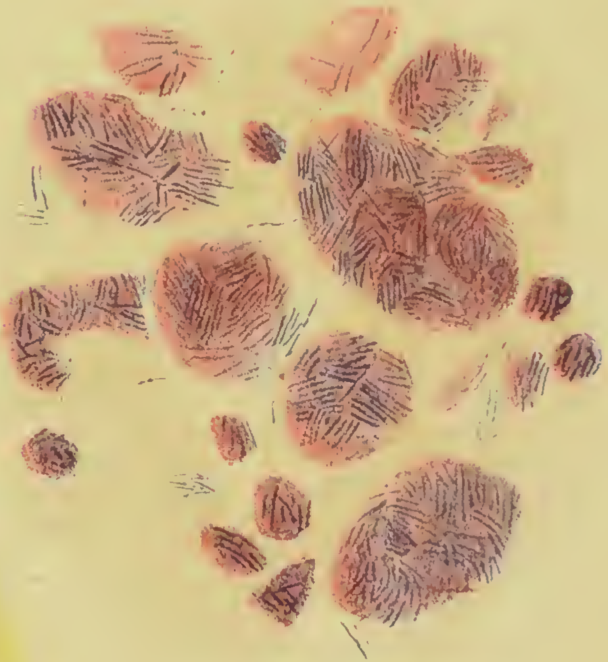

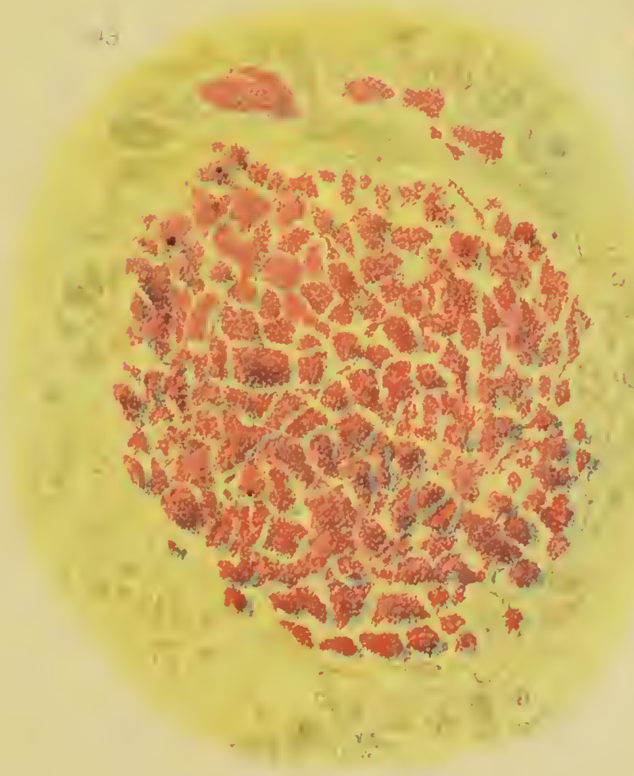

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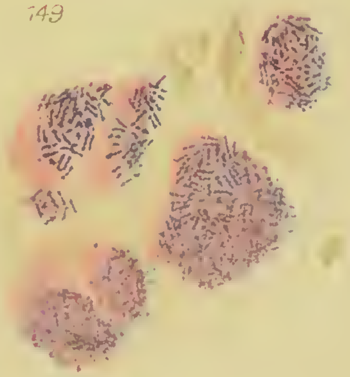


PLATE XXV

FIG.

150. From a section through an actinomyces nodule in the tongue of ox. The centre shows the actinomyces with its radiating clubs. Rubin and then methyl blue. Magnifying power, 500.

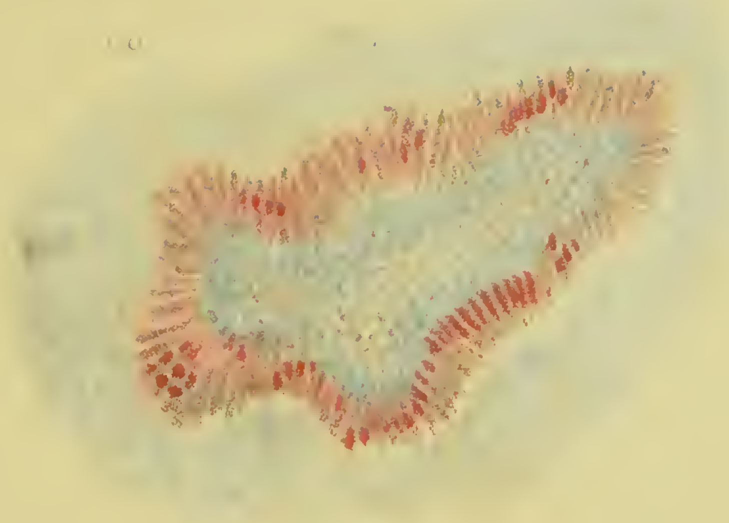
151. From the same specimen, showing in surface view part of an actinomyces clump. The red dots are the 'clubs' seen in bird's-eye view. Magnifying power, 500.

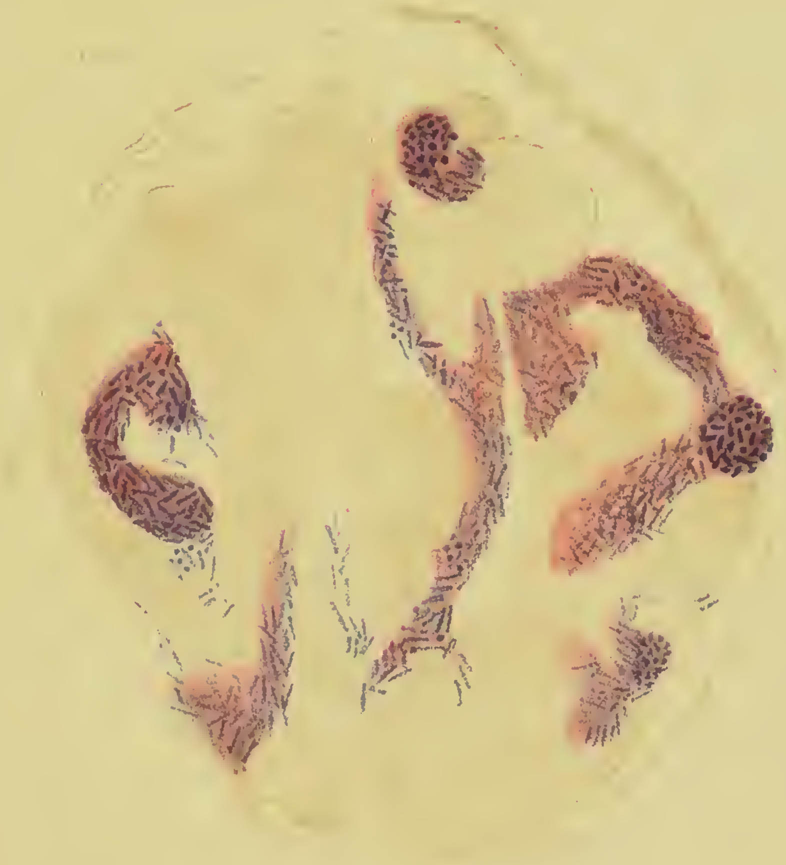
152. A Malpighian corpuscle of the kidney of a person dead after meat poisoning at Welbeck. Some of the capillaries of the glomerulus are plugged with masses of bacilli, the remainder of the glomerulus swollen, and showing hyaline degeneration. Gentian violet staining. Magnifying power, 500.

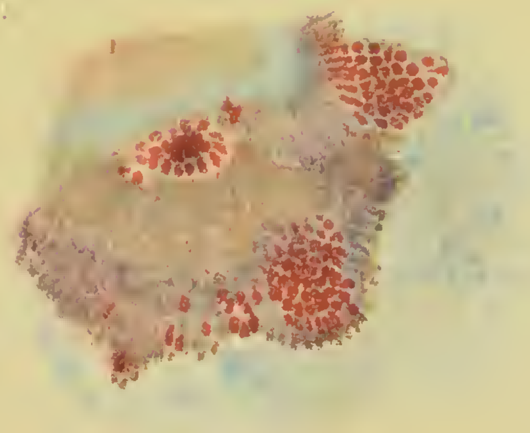
(Treatise on Hygiene)
Vol. II

PLATE V

[Klein]







West Newman Lith.

Plates XXVI–XXX inclusive. Figs. 1 to 46 are from photograms made by Mr. E. C. Bousfield, except figs. 35, 37, and 38. All of natural size.

PLATE XXVI

Fig.

1. Plate cultivation of air of Wandsworth Common.

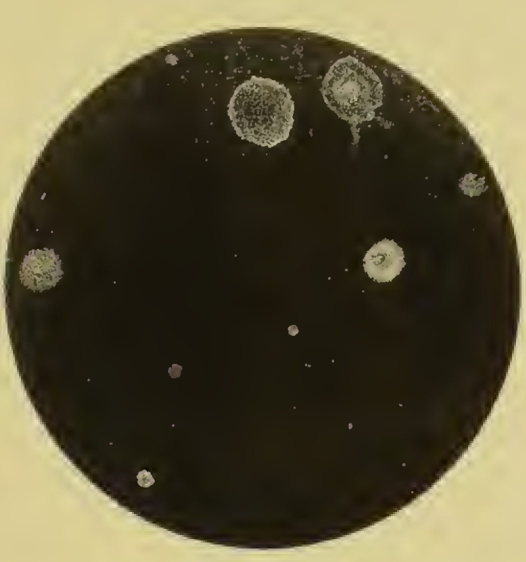
2. Plate cultivation of air of Oxford Street. Both plates are on gelatine, which after it was set was exposed for three minutes to the air, the difference between the time of exposure at Wandsworth Common and in Oxford Street being about one hour. Date, March 1891. The difference in the number of colonies, that is, in the number of micro-organisms, in the two localities is striking.

3. Plate cultivation in gelatine of Finkler's comma bacilli; some of the colonies isolated, others confluent, all liquefying the gelatine.

4. Plate cultivation in gelatine of the aërobic bacillus of malignant œdema. The small dots are colonies in the depth, the large patches are the colonies growing on the surface.

5. Plate cultivation in gelatine of a quarter of a cubic centimetre of the ordinary standpipe water of the West Middlesex Water Company; three colonies per $\frac{1}{4}$ c.c., that is, 12 per 1 c.c.

6. Plate cultivation in same manner of water of Grand Junction Water Company, about eight colonies per $\frac{1}{4}$ c.c.



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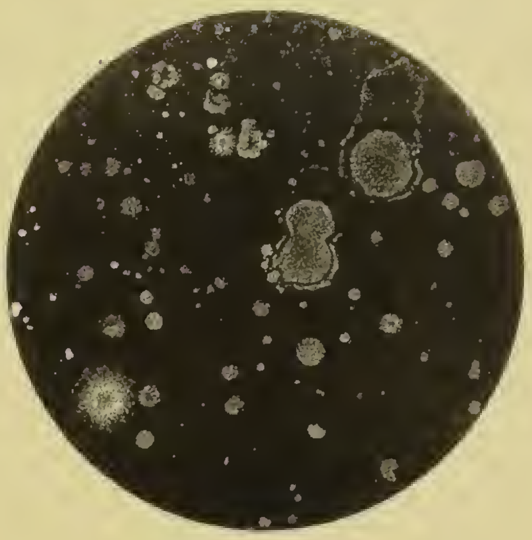

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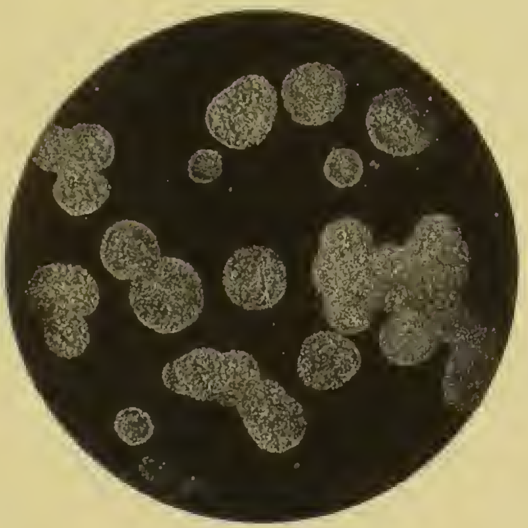

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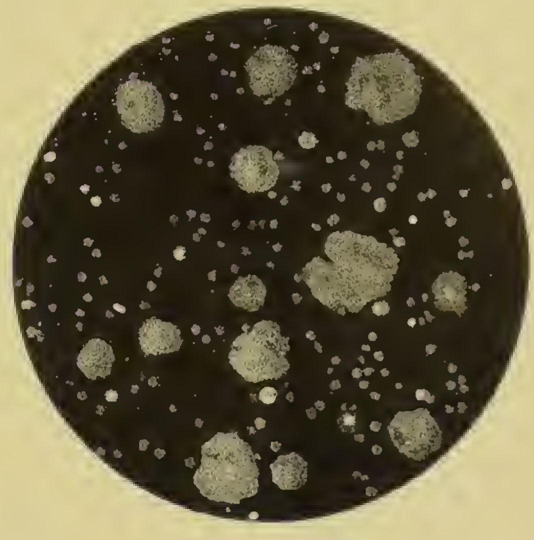

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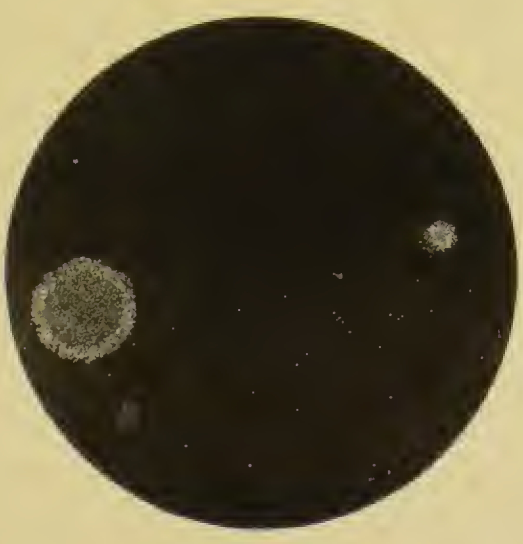

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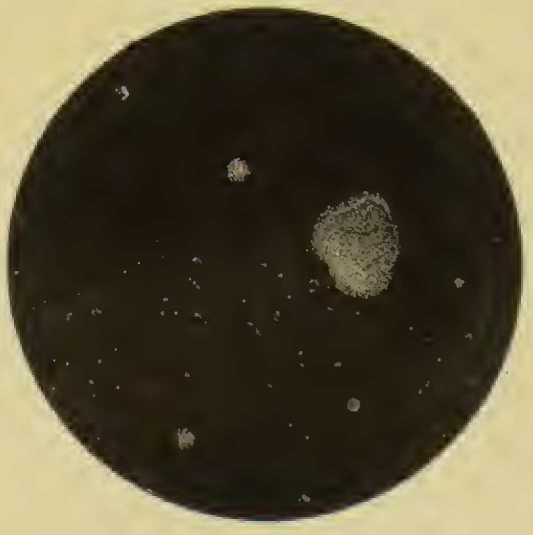

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West, Newman lith

PLATE XXVII

FIG.

7. Streak culture on the surface of slanting gelatine of fowl cholera.

8. Ditto of fowl enteritis.

9. Ditto of the typhoid bacillus.

10. Ditto of the bacillus of Middlesbrough pneumonia.

11. Ditto of the bacillus of grouse disease.
(All these five cultures are of the same age.)

12. Streak culture, on the surface of slanting gelatine, of the streptococcus of the Edinburgh disease.

13. Ditto of streptococcus scarlatinæ.

14. Ditto of streptococcus pyogenes.

15. Ditto of streptococcus erysipelas. This last photo does not correctly represent the actual appearances, being too much of a homogeneous character.
(All these four streptococcus cultures of same age.)

16. Streak culture on gelatine of the pie bacillus of Portsmouth pie poisoning, two days old.

17. Ditto six days old.

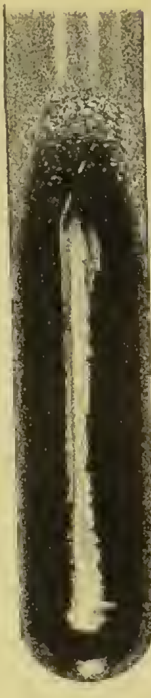
18. Broth culture of staphylococcus aureus, the broth uniformly turbid after twenty-four hours at 37° C.

19. Broth culture of the bacillus of Middlesbrough pneumonia, after twenty-four hours.

20 Stab culture in gelatine of bacillus fluorescens liquescens. The upper part of the gelatine liquefied by the growth.

Pl. XXVII.

7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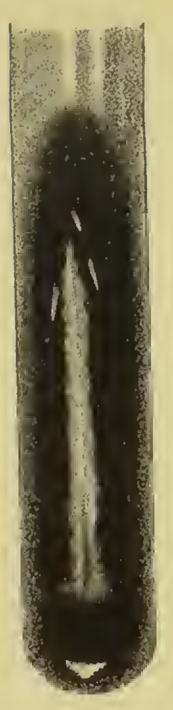
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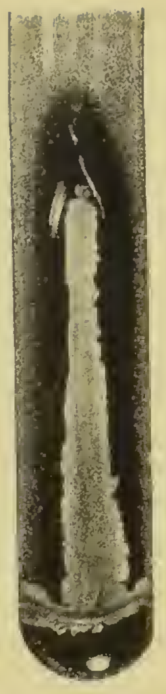
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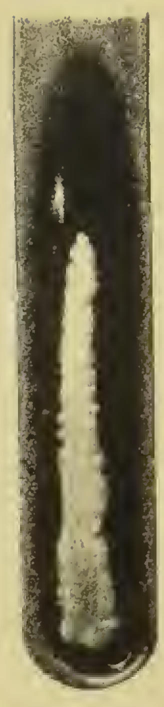
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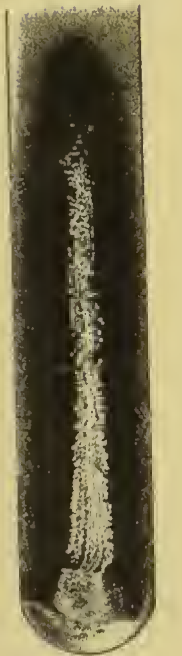
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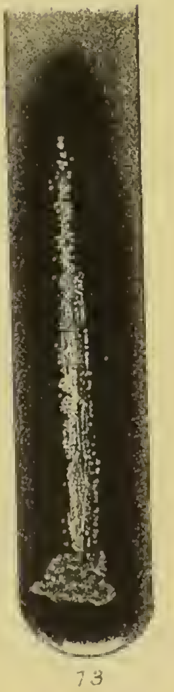
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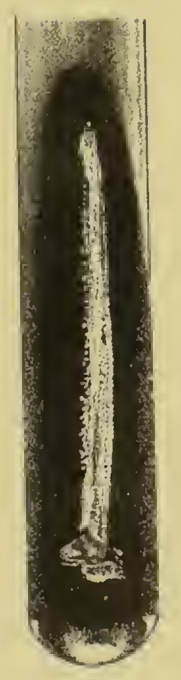
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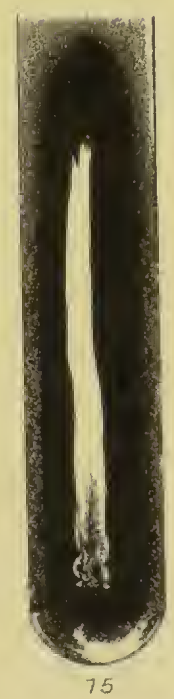
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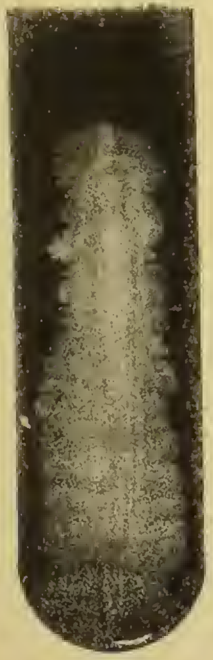
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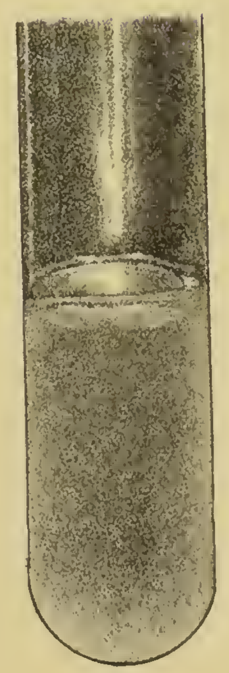
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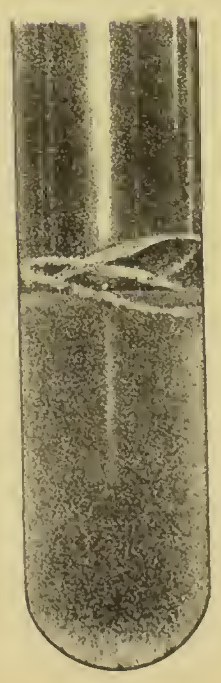
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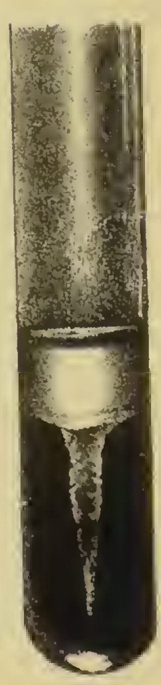
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West, Newman lith.

PLATE XXVIII

FIG.

21. Stab culture in gelatine of the bacillus of swine erysipelas.

22. Stab culture in gelatine of bacillus anthracis. The upper part of the growth has commenced to liquefy the gelatine.

23. Stab culture in gelatine of the aërobic bacillus of malignant œdema. A number of flat gas bubbles are attached to the streak growth.

24. Shake culture in gelatine of the aërobic bacillus of malignant œdema. Numerous gas bubbles in connection with the dot-like colonies.

25 and 26. Shake cultures in gelatine of the aërobic bacillus of malignant œdema from the blood of rabbit and mouse respectively, dead after inoculation.

27. Streak cultures on the slanting surface of gelatine of the bacillus diphtheriæ of the human subject.

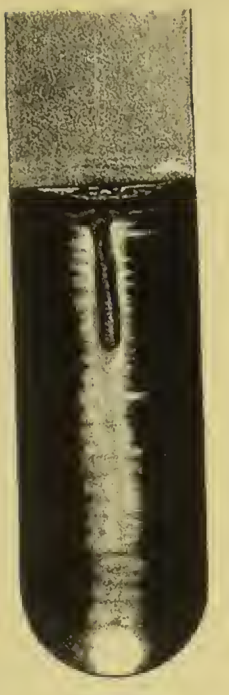
28. The same bacillus forming isolated colonies on the slanting surface of gelatine—tube plate cultivation.

29. The same bacillus forming colonies on the surface of gelatine, after two weeks' incubation.

30. A pseudo-diphtheria bacillus, derived from cow's milk, forming colonies on the slanting surface of agar.

31. Streak culture on agar of the same pseudo-diphtheria bacillus as in fig. 30.

32. Stab culture in gelatine of the bacillus of Portsmouth pie, the same as in 16 and 17 of Plate XXVII.



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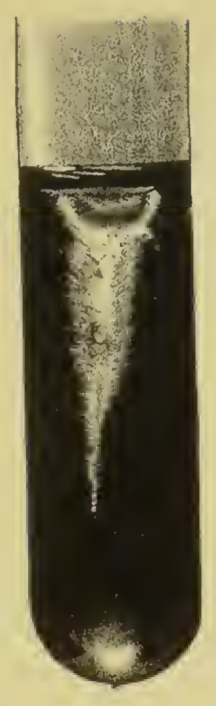

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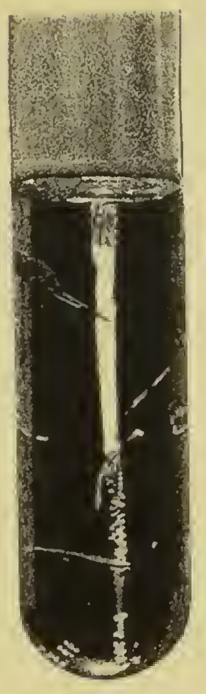

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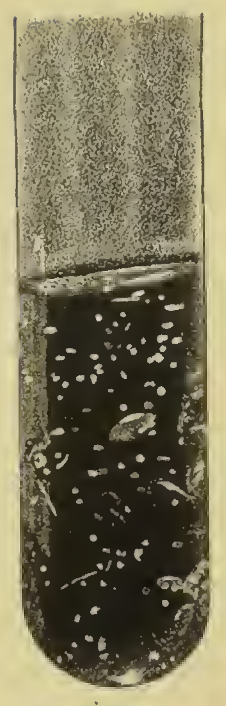

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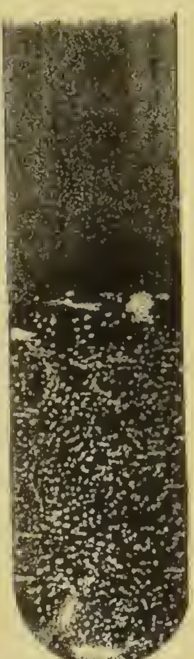

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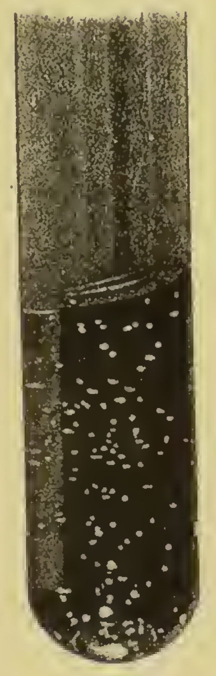

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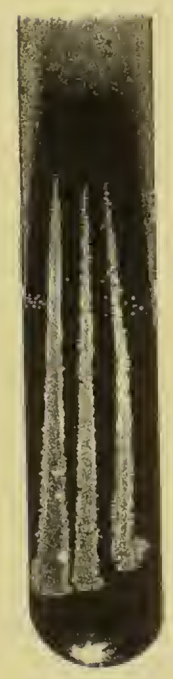

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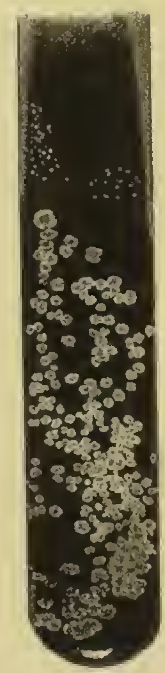

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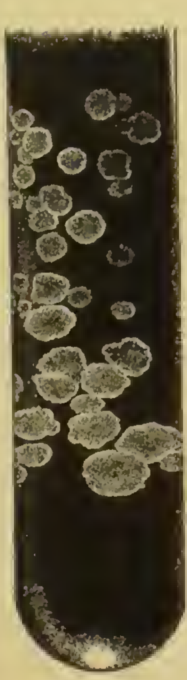

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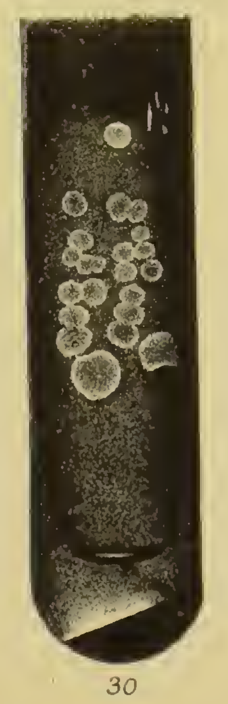

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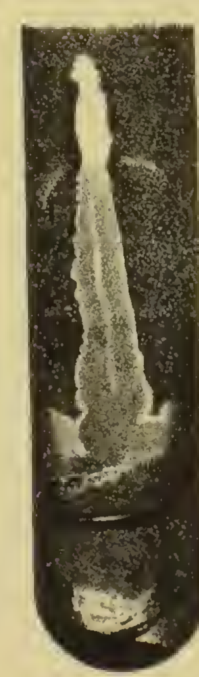

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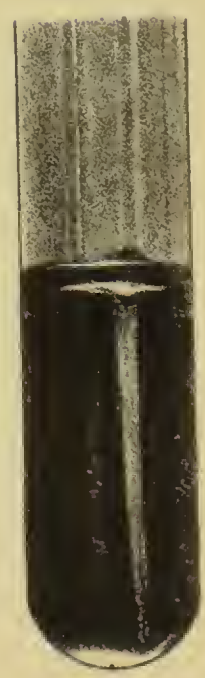

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West, Newman lith.

PLATE XXIX

FIG.

33. Stab culture in gelatine of the bacillus diphtheriæ derived from the (human) diphtheritic membrane. The culture is several weeks old.

34. Similar culture of the bacillus diphtheriæ derived from the diphtheritic necrotic tumour of the cow, artificially produced by subcutaneous inoculation.

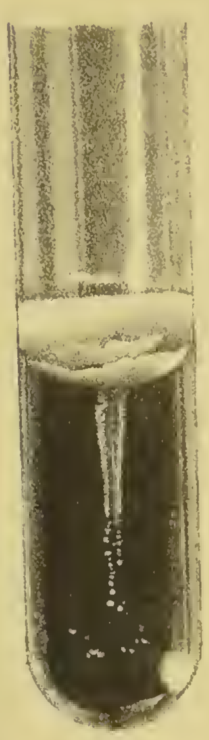
35. Plate cultivation in gelatine of Koch's cholera spirilla, seventy-two hours old. Magnified fifty times. Copied from Plagge.

36. Cultivation of Koch's anaërobic bacillus of milignant œdema in grape sugar gelatine. The growth (in the depth) has liquefied the gelatine. Numerous gas bubbles are noticed.

37. Cultivation of the tetanus bacillus in the depth of grape sugar gelatine, six days old. Copied from Fränkel and Pfeiffer's Atlas, Plate XXVII, fig. 55.

38. Cultivation of the bacillus of symptomatic charbon in the depth of grape sugar gelatine, four days old. Copied from Fränkel and Pfeiffer's Atlas, Plate XXVIII, fig. 57.

Pl. XXIX.



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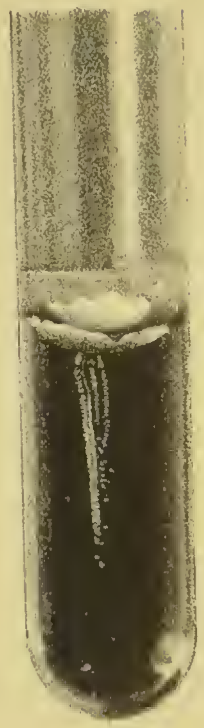

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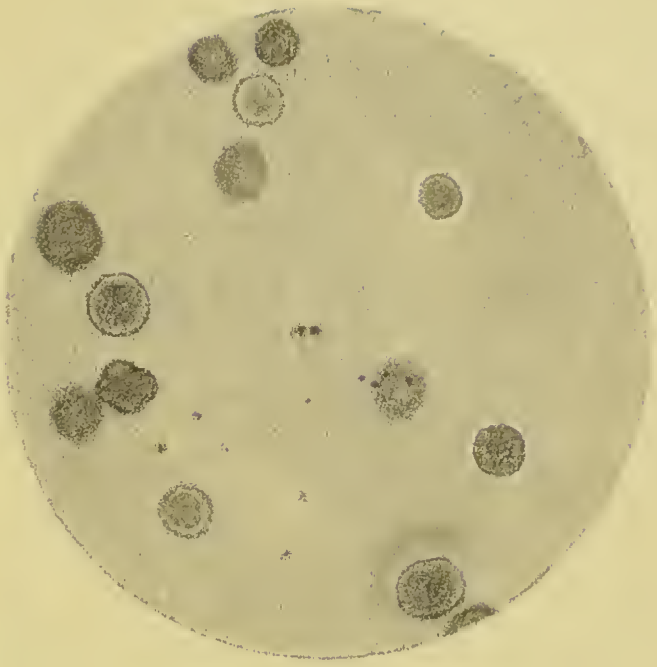

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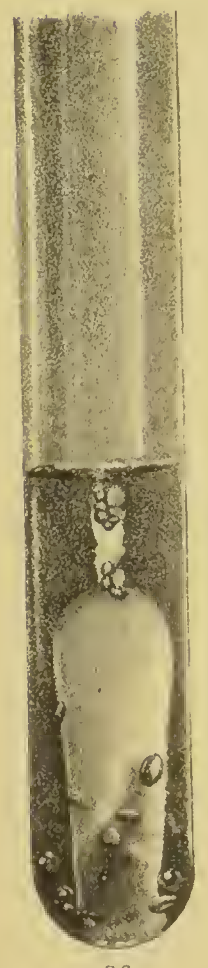

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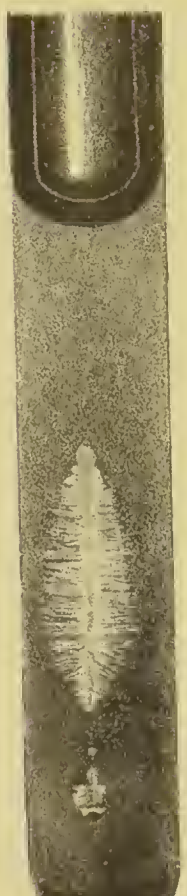

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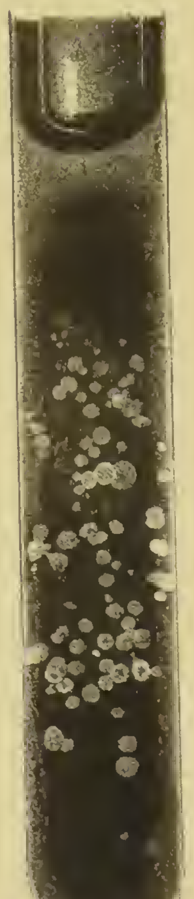

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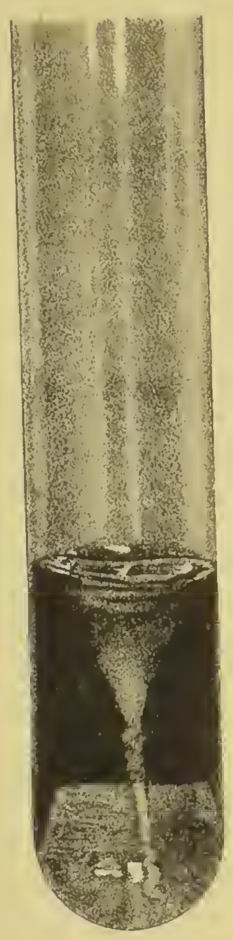
West, Newman lith

PLATE XXX

Figs.

39–46. Cultivations (stab) in gelatine of different varieties of choleraic comma bacilli. All the cultures have been incubated for nine days at 20° C. The amount of growth and the amount of liquefaction by them of the gelatine at the upper part of the stab differ in the different species.



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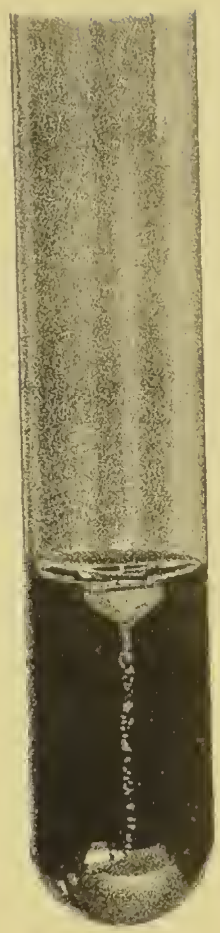

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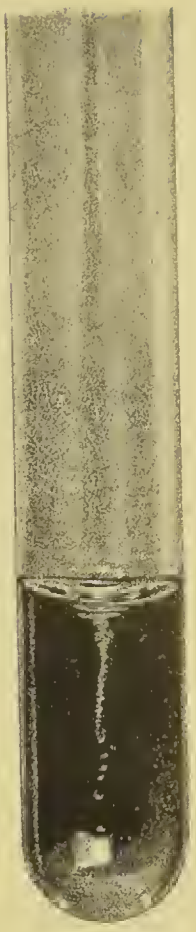

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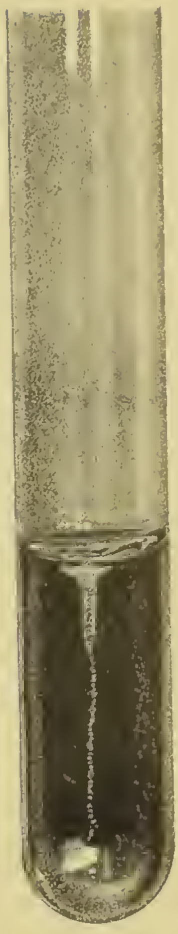

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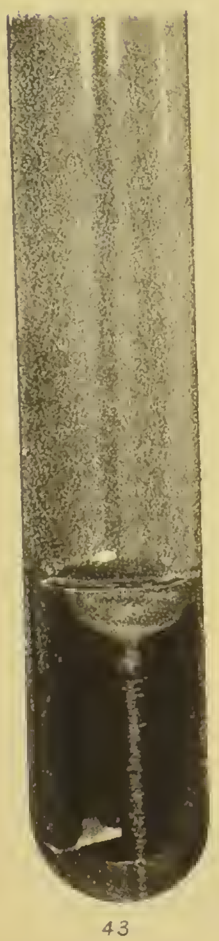

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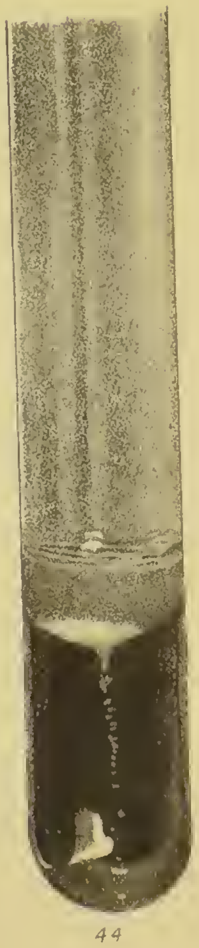

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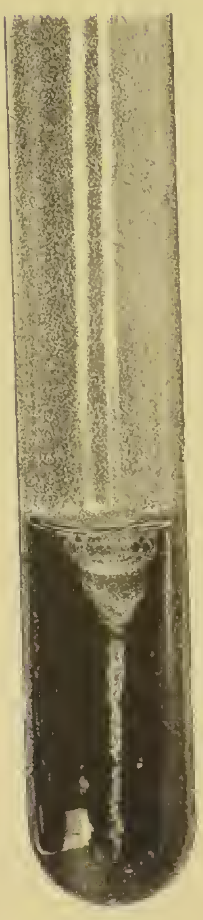

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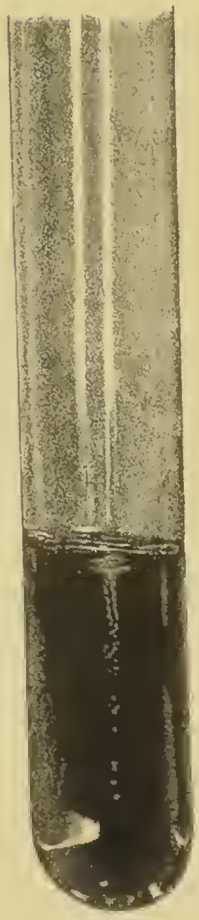

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West, Newman lith.

PLATES XXXI–XXXIX inclusive are from drawings by Mr. M. H. LAPIDGE.

PLATE XXXI

FIG.

47. Plate cultivation in gelatine of bacillus anthracis, after three days' incubation at 20° C. The colonies are seen in transmitted light as angular masses, numerous bundles of threads passing between them. Magnifying power, 10.

49. Plate cultivation of the bacillus of swine fever, seen in transmitted light, after twelve days' incubation at 20° C. Each colony is marked as a circular or slightly irregular patch with clear centre. Magnifying power, 10.

50. Colonies of the glanders bacilli on the surface of agar, seen in transmitted light after nine days' incubation at 37° C. Each colony is a flat disc, dark granular in the centre. Magnifying power, 10.

51. Colonies of the bacillus of Middlesbrough pneumonia, on the surface of gelatine, seen in transmitted light, after forty-eight hours' incubation at 20° C. Magnifying power, 10.

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PLATE XXXII

FIG.

52. Colonies of the bacillus diphtheriæ on gelatine, seen in transmitted light, after ten days' incubation at 20° C. Magnifying power, 10.

53. Same after three weeks' incubation. Magnifying power, 10.

48. Colonies of the bacillus of fowl enteritis on gelatine, seen in transmitted light, after several days' incubation at 20° C. Magnifying power, 8.

56. Colonies of the bacillus diphtheriæ on the slanting surface of agar, seen in transmitted light, incubated two weeks at 36–37° C. Natural size. The lithographic representation is not quite correct, the centre of the colonies being less knob-like, as here represented, and more yellow brown.

61. Streak culture on gelatine of micrococcus aurantiacus, after a week's incubation at 20° C. Natural size.

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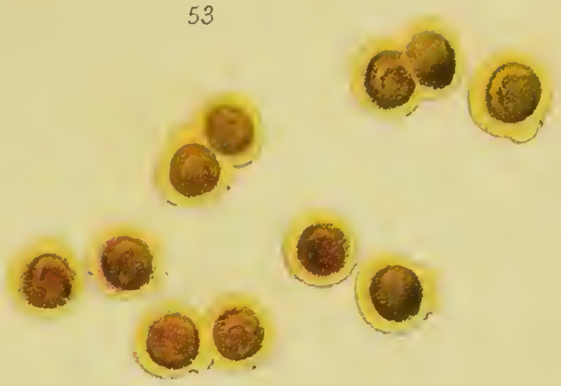

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PLATE XXXIII

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.

54. Colonies of the glanders bacillus on the surface of agar, after nine days' incubation, at 37° C.

55. Colonies of the diphtheria bacillus on agar, after two weeks' incubation.

57. Colonies of the Middlesbrough pneumonia bacillus on gelatine, one week's incubation.

58. Colonies of the bacillus of fowl enteritis on gelatine, one week's incubation.

59. Colonies of the typhoid bacillus of Eberth-Gaffky on gelatine, after one week's incubation.

60. Colonies of the bacillus of grouse disease on gelatine, after one week's incubation.

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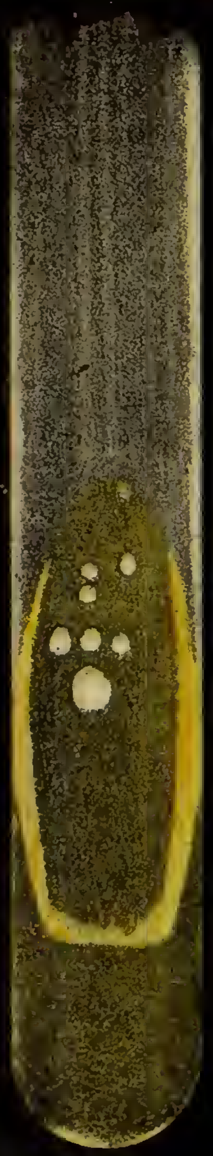

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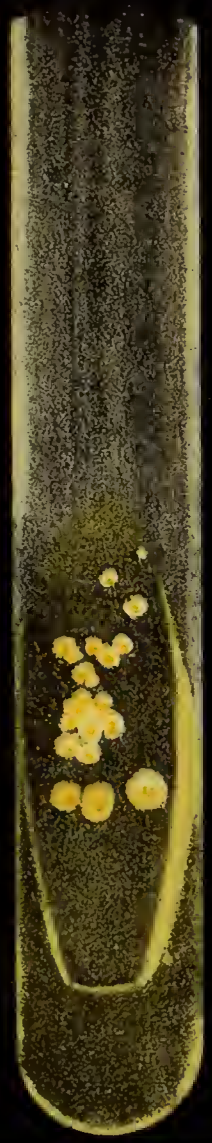

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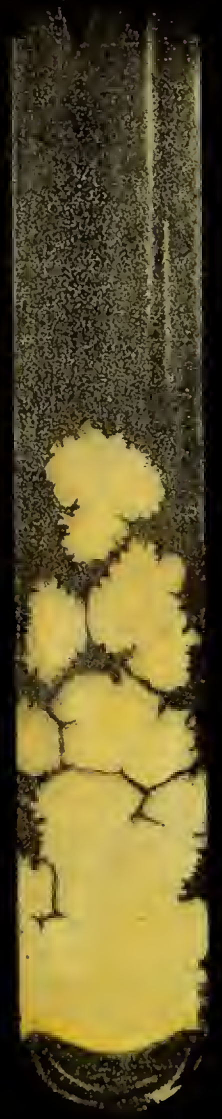

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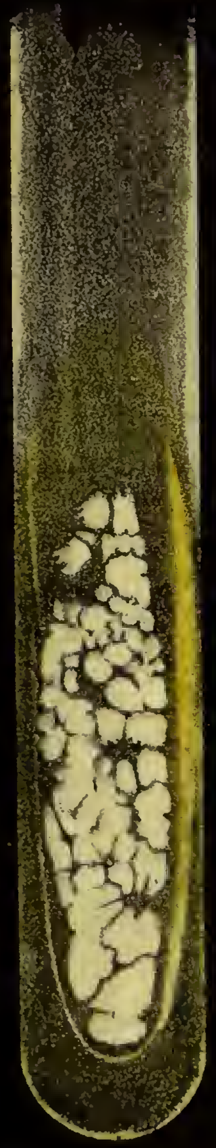

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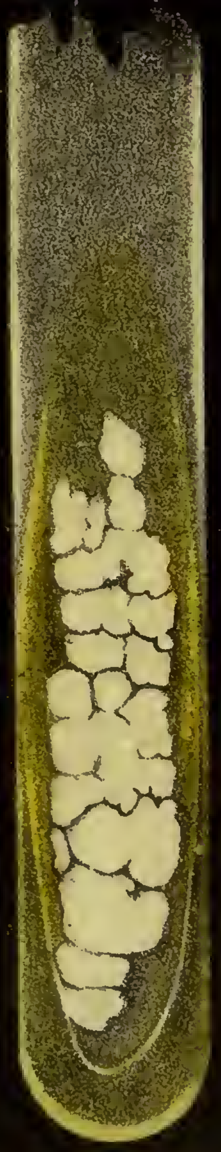

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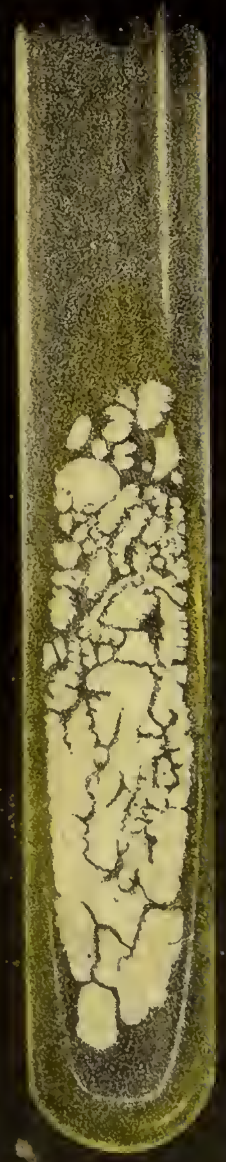

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West, Newman chr. lith.

PLATE XXXIV

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.
62. Streak culture on gelatine of the bacillus of pork-pie poisoning.

63. Streak culture on agar of the staphylococcus aureus (37° C.).

64. Streak culture of bacillus pyocyaneus on agar (37° C.).

65. Streak culture on gelatine of the bacillus of Middlesbrough pneumonia.

66. Streak culture on gelatine of the bacillus diphtheriæ.

67. Streak culture on agar of the bacillus prodigiosus (20° C.).

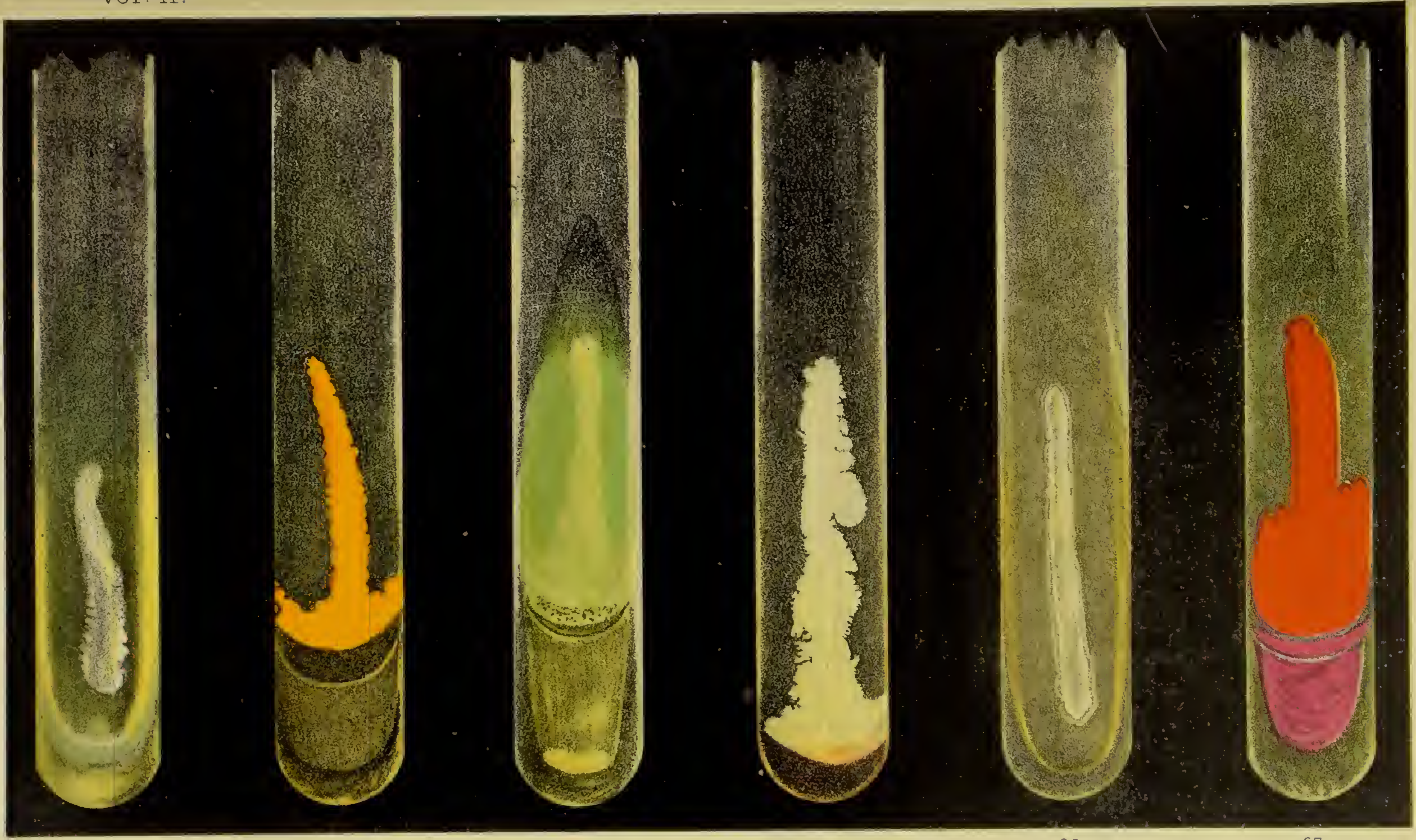

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PLATE XXXV

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.

68. Surface cultivation on glycerine agar of the tubercle bacillus after five months (37° C.).

69. Similar cultivation after nine months (37° C.).

70. Stab culture in gelatine of the bacillus of Middlesbrough pneumonia.

71. Stab culture in gelatine of the staphylococcus albus liquescens, after three days' incubation, at 20° C.; liquefaction of the gelatine very marked.

72. Stab culture in gelatine of Finkler's comma bacillus after about three days.

73. Stab culture in gelatine of the bacillus pyocyaneus after three days.

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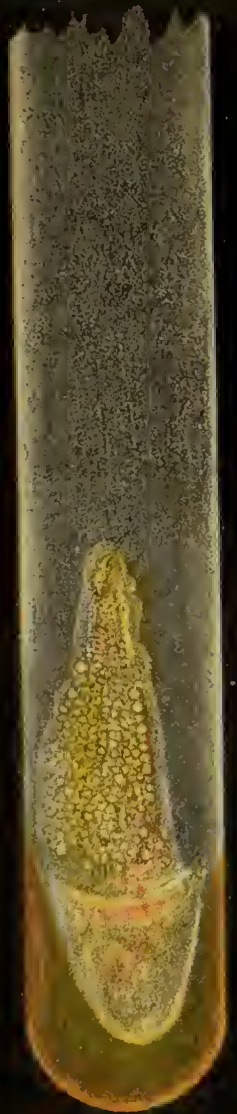

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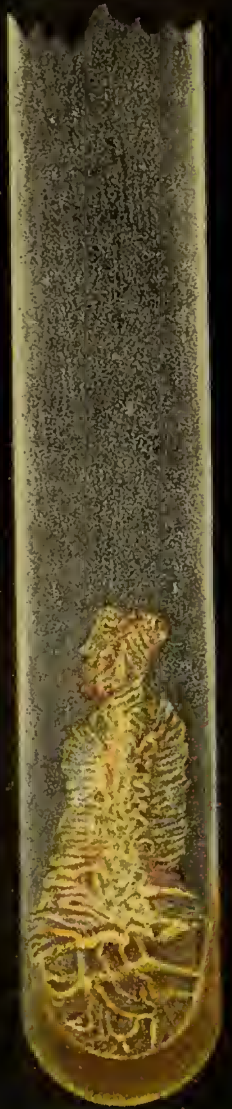

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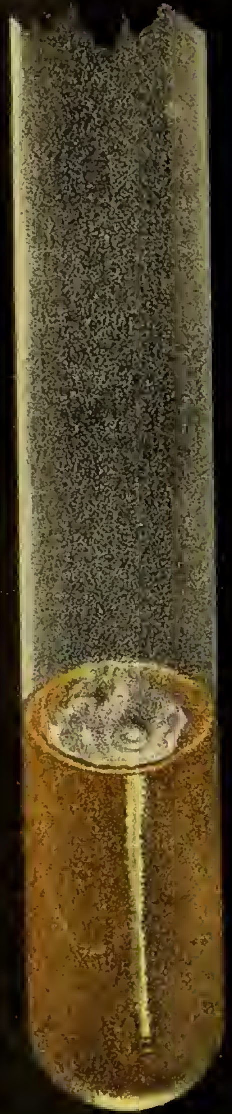

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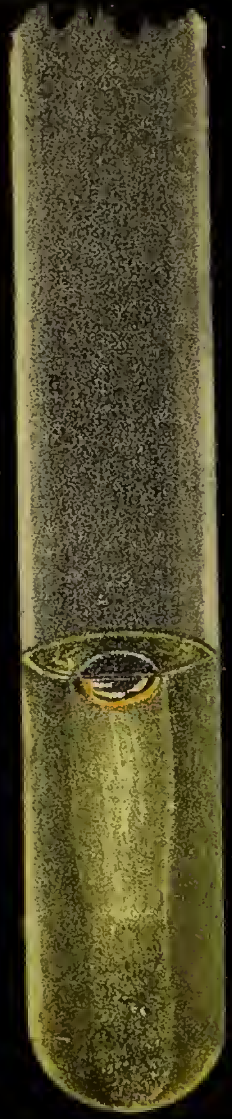

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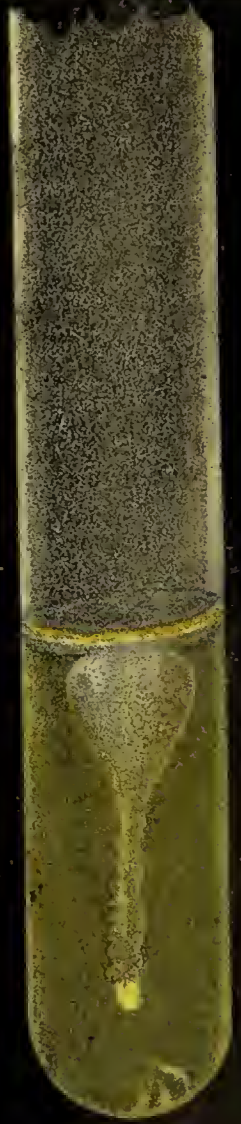

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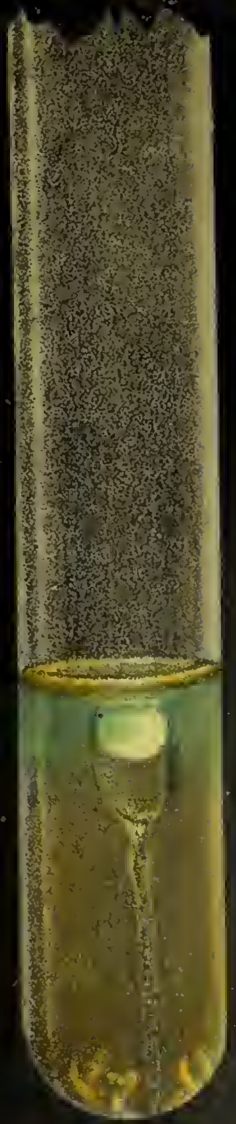

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PLATE XXXVI

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.

74. Stab culture in gelatine of the bacillus fluorescens liquescens, after seven days.

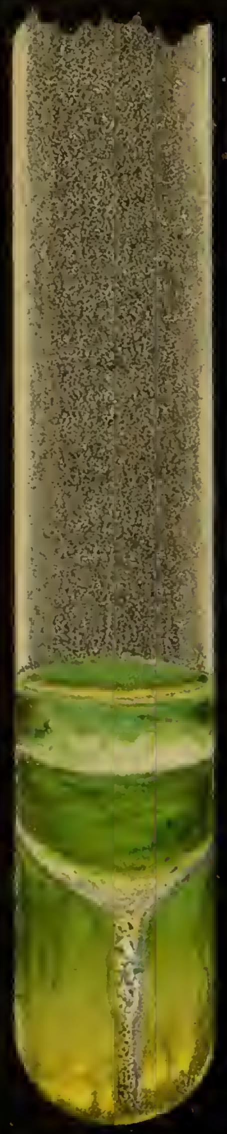
75. Stab culture in broth gelatine of the glanders bacillus, after seventeen days' incubation, at 22° C.

76. Same after twenty-three days. Slight liquefaction has commenced at the upper end of the stab.

77. Stab culture in gelatine of the bacillus of swine erysipelas, after fourteen days.

78. Stab culture in gelatine of the bacillus anthracis, after seven days. Liquefaction has commenced at the upper end of the stab.

79. Same after fourteen days. Liquefaction on the surface is more pronounced.



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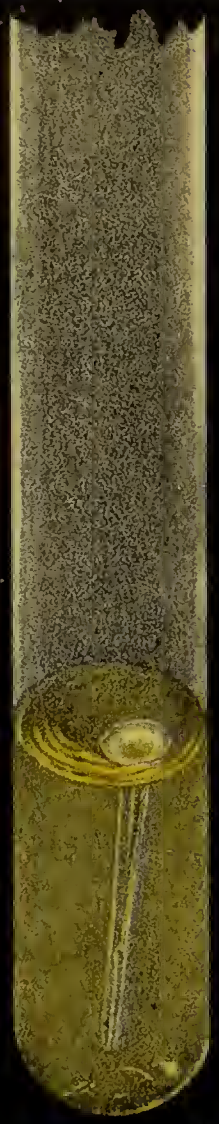

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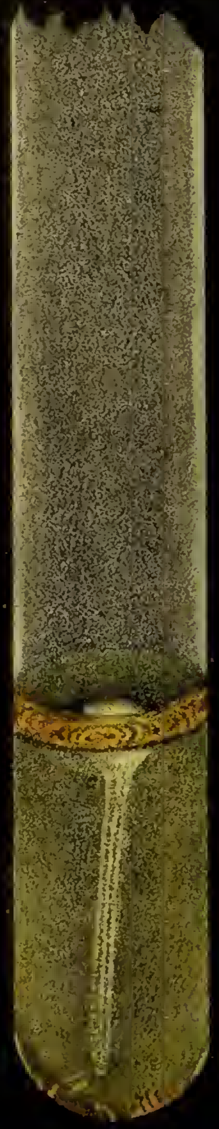

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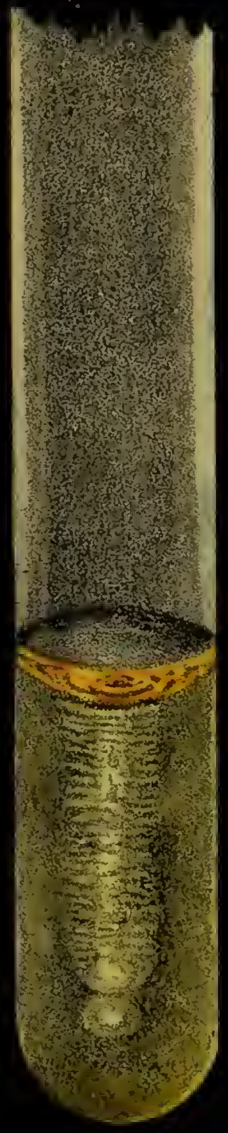

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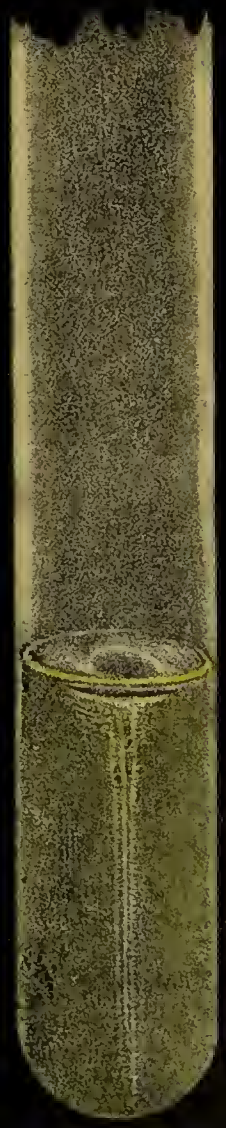

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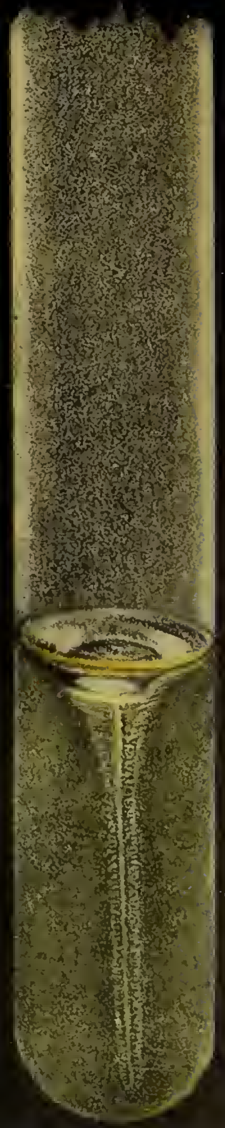

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West, Newman chr lith

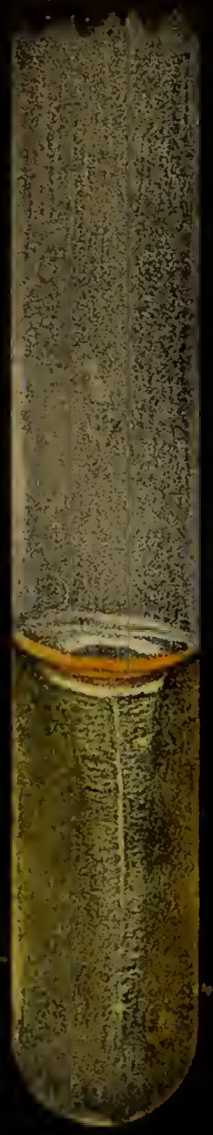
PLATE XXXVII

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.

80. Stab culture in gelatine of bacillus anthracis after seven days. Liquefation at the surface has commenced.

81, 82, 83, 84, and 85 are stab cultures in gelatine of different varieties of cholera spirilla, all after eight days' incubation, at 20° C. They all show the funnel-shaped depression on the surface, and in all liquefaction of the gelatine is proceeding; but the amount of growth and the rapidity of liquefaction are different in the different varieties.



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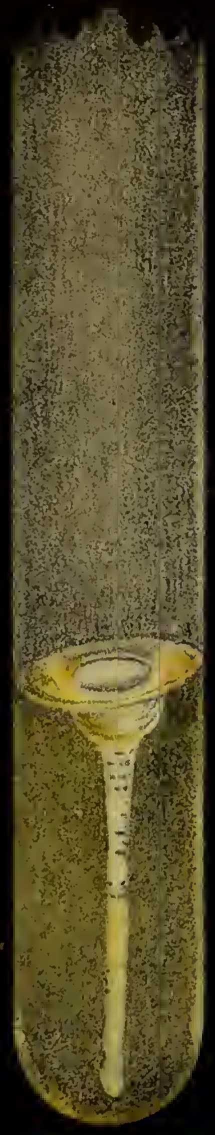

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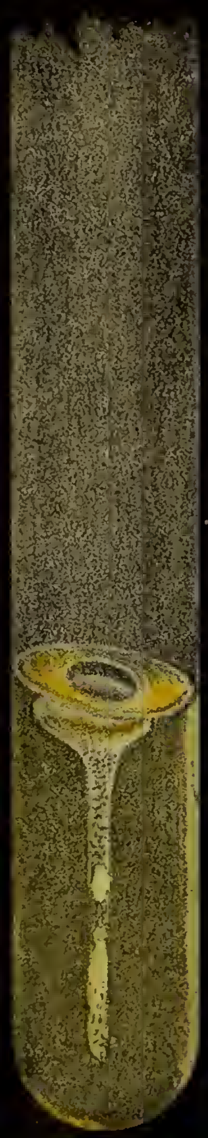

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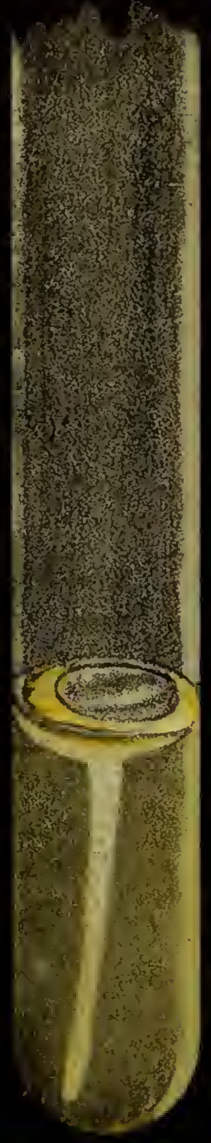

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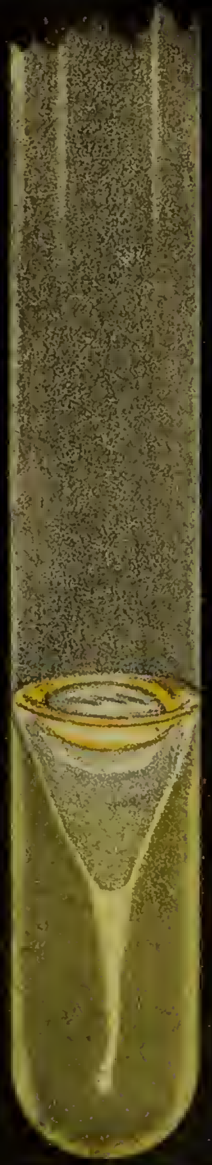

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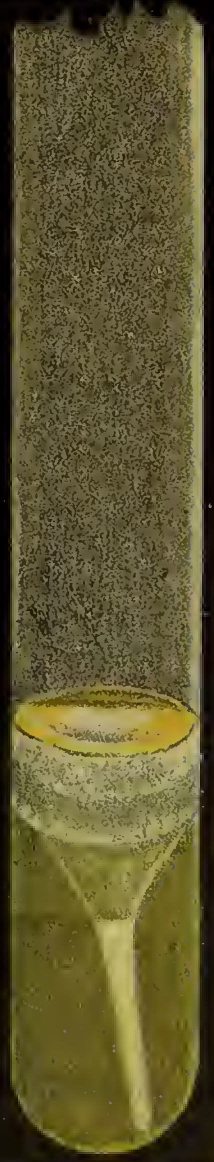

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PLATE XXXVIII

TUBE CULTIVATIONS, NATURAL SIZE, SEEN IN REFLECTED LIGHT

Fig.

86. A further variety of the cholera spirilla, belonging to the series shown in Plate XXXVII. This last one corresponds to the one described by Koch.

87. Culture on potato of the sarcina lutea.

88. Culture on potato of a bacillus of chronic necrotic deposit in the membrane of the fauces of fowl.

89. Culture on potato of bacillus prodigiosus.

90. Culture on potato of bacillus of glanders, after fourteen days' incubation.

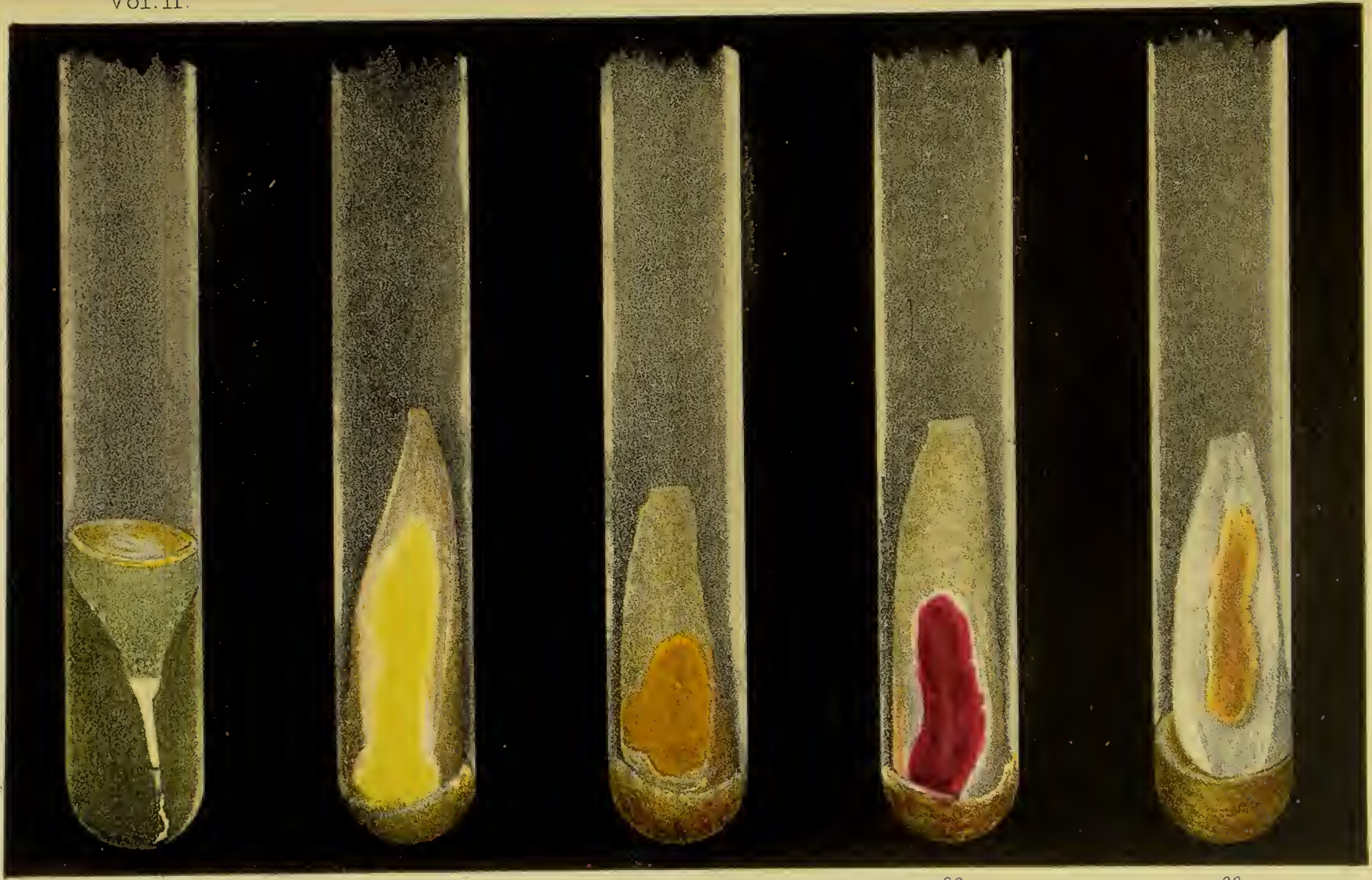

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PLATE XXXIX

POTATO CULTURES IN TUBES, NATURAL SIZE, SEEN IN REFLECTED LIGHT

FIG.

91. Cultivation of bacillus of glanders, after twenty-six days. This is a companion cultivation to that shown in fig. 90 of Plate XXXVIII, after fourteen days' incubation.

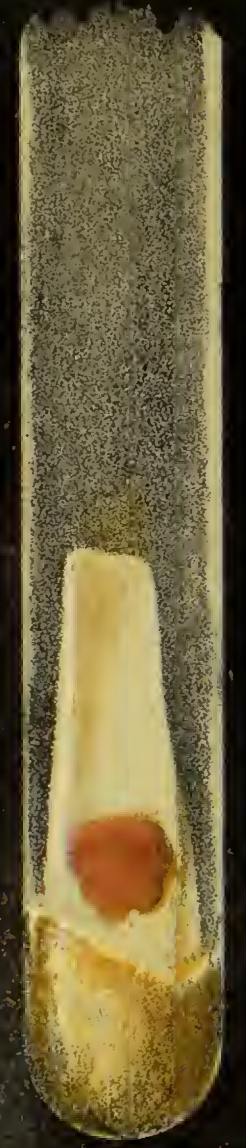
92, 93, 94, and 95. Cultivations on potato of different varieties of cholera spirilla.

92 corresponds to the variety shown in gelatine culture 86.

93 corresponds to the variety shown in gelatine culture 81.

94 corresponds to the variety shown in gelatine culture 83.

95 corresponds to the variety shown in gelatine culture 85.



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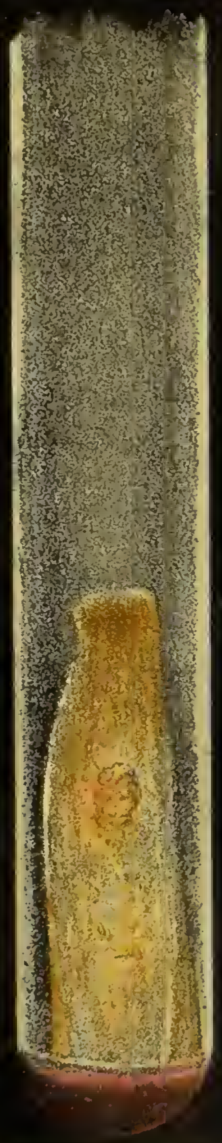

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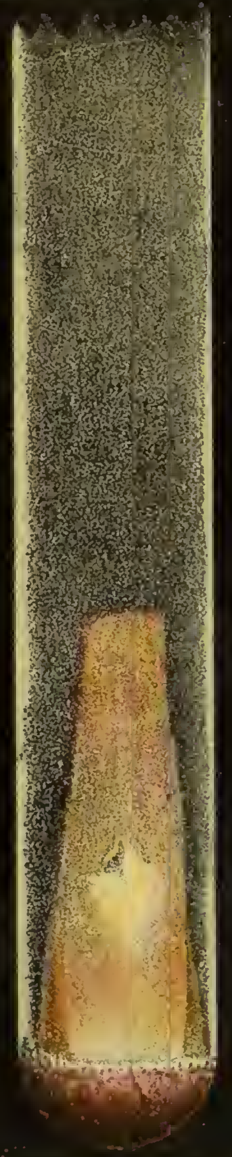

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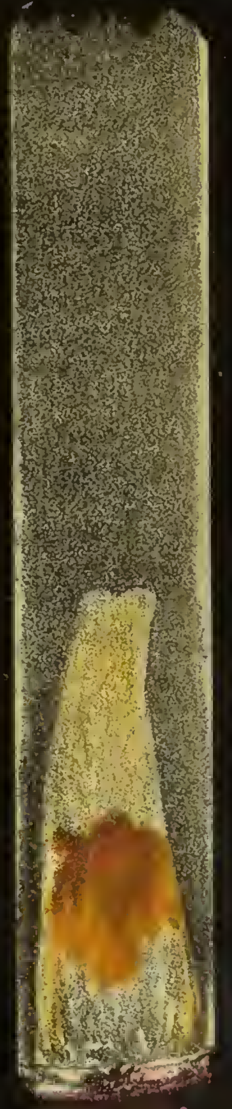

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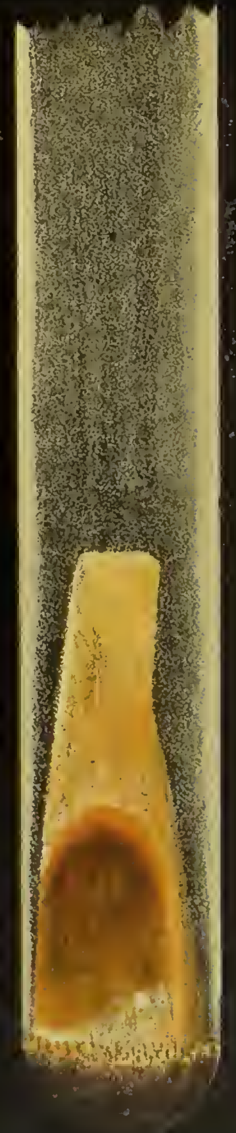

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PLATE XL

Fig.

99. Oïdium lactis, mycelium, and spores. Copied from Klein's 'Micro-organisms and Disease,' fig. 114.

100. Saccharomyces mycoderma (after Gravitz) from an artificial cultivation in dilute nutritive material: (*d*) branched mycelium; (*f*) *a*, torula stage; *β*, mycelial stage. Copied from Klein's 'Micro-organisms and Disease.'

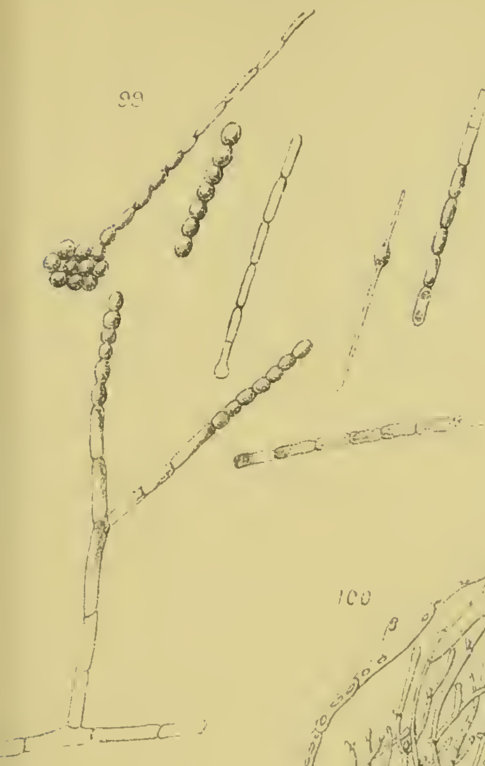
106. From a section through the kidney of a rabbit dead thirty-six hours after the injection of aspergillus spores into the jugular vein (after Gravitz). T, Tyrosin crystals; F, fat droplets. In the upper part of the figure is a metastatic focus, composed of spores and mycelium, numerous fat droplets amongst them. In the lower part the uriniferous tubules and two Malpighian corpuscles are shown. Copied from Klein's 'Micro-organisms and Disease,' fig. 118.

104. Aspergillus glaucus (after De Bary). A, hypha. At the end, at *c*, it bears *st*, the basidia; *as*, ascogonium.

105. E, perithecium; *as*, ascogonium; *w*, cells of the pollinodia. Copied from Klein's 'Micro-organisms and Disease,' figs. 116 and 117.

107. Saprolegnia of salmon disease. The figure represents a sporangium filled with zoospores; in connection with it are several young mycelial threads, marked by their coarsely granular dark protoplasm. Copied from Klein's 'Micro-organisms and Disease,' fig. 119.

99



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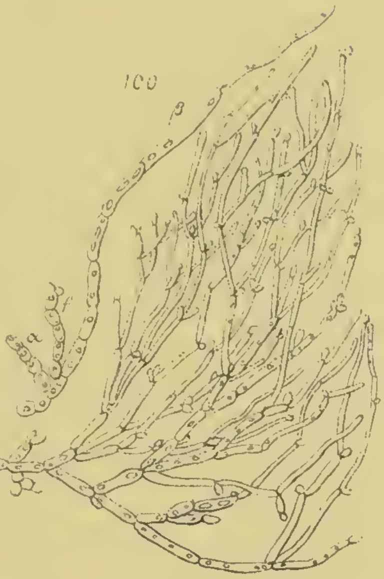

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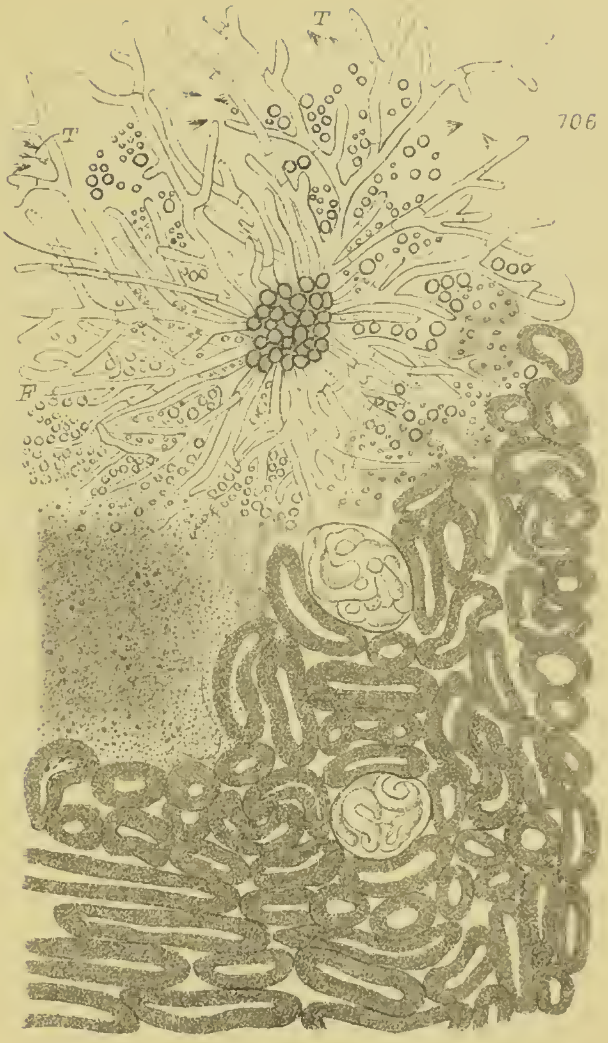

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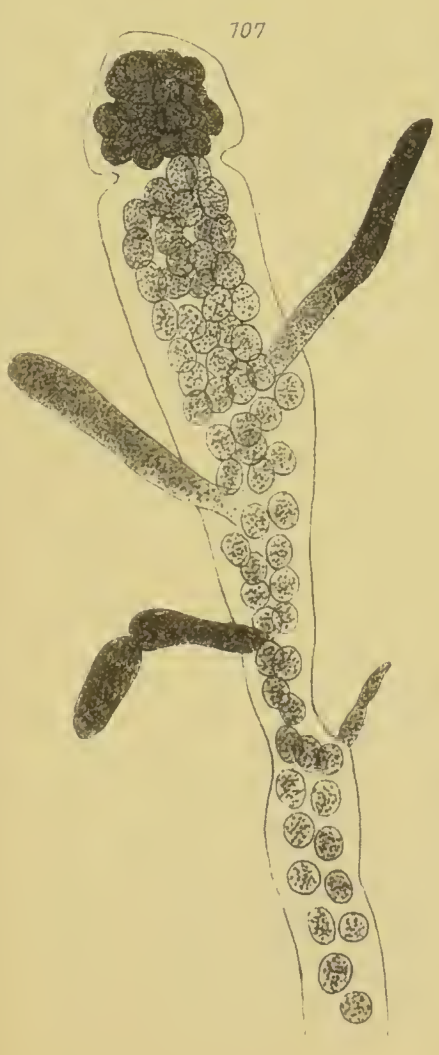

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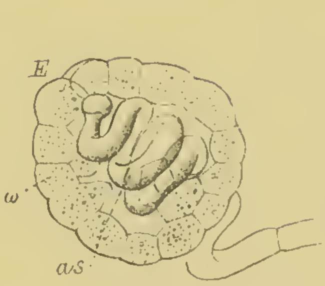

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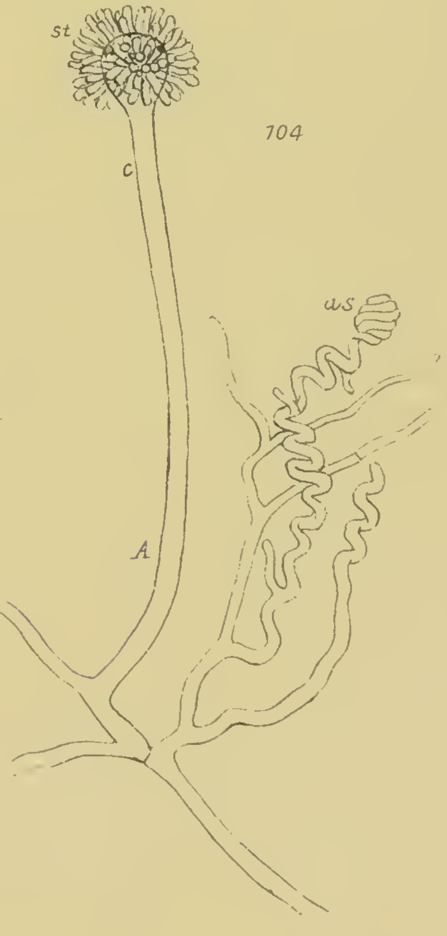

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PLATE XLI

Fig.

101. Herpes fungus, mycelium, and spores, after Gravitz, copied from Flügge's 'Mikroorganismen,' fig. 17.

103. Mucor corymbifer, hyphæ and sporangia, after bursting of the membrane of the sporangia. After Lichtheim, copied from Flügge's 'Mikroorganismen,' fig. 21 *b*.

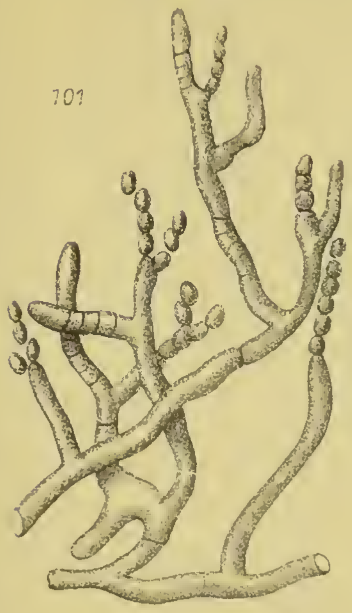
98. Torula or saccharomyces. In the lower part of the figure ascospores and four isolated spores (after Rees) are shown. Copied from Klein's 'Micro-organisms and Disease,' fig. 112.

102. Penicillium glaucum : (*m*) mycelium ; from it rise non-septate hyphæ bearing at their ends the spores. Copied from Flügge's 'Mikroorganismen,' fig. 22.

96. Amœba coli in mucus of intestine. Numerous blood-corpuscles and degenerated epithelial cells are also seen. After Lösch, copied from Leuckart's 'Die Parasiten des Menschen,' I., 1, p. 235, fig. 94.

97. Coccidium oviforme from the liver of rabbit seen 550 times magnified. *c* to *g*, progressive changes during the formation of spores, observed only outside the animal body. Copied from Leuckart's 'Die Parasiten des Menschen,' I., 1, p. 256, fig. 106.

101



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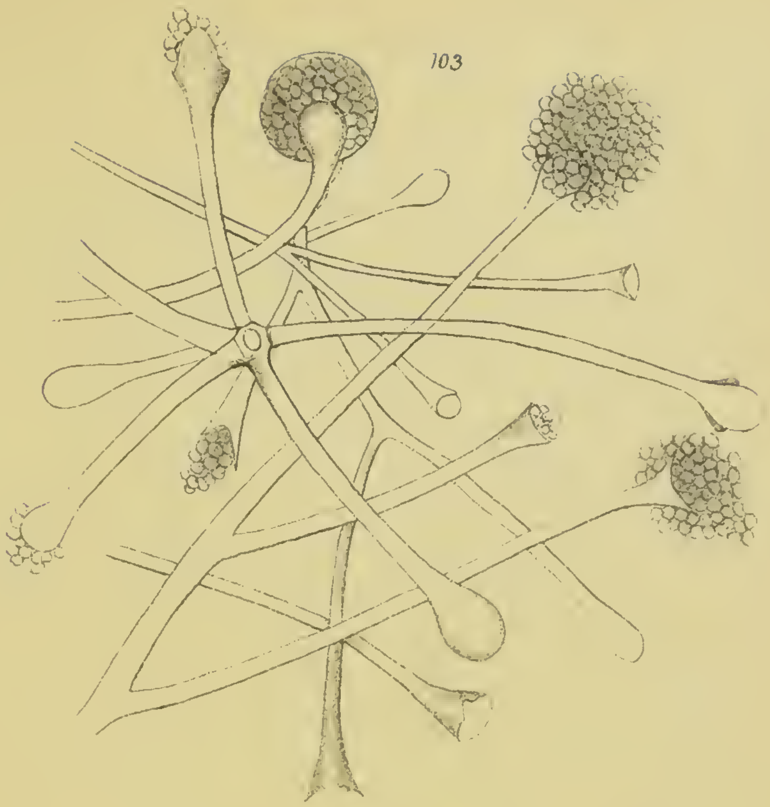

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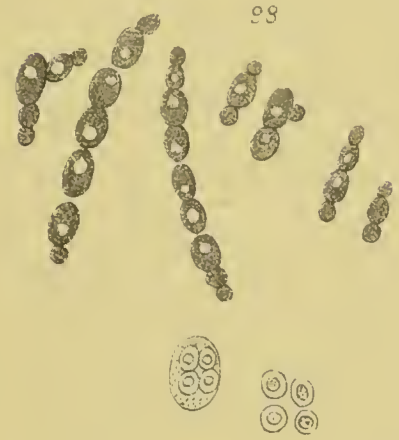

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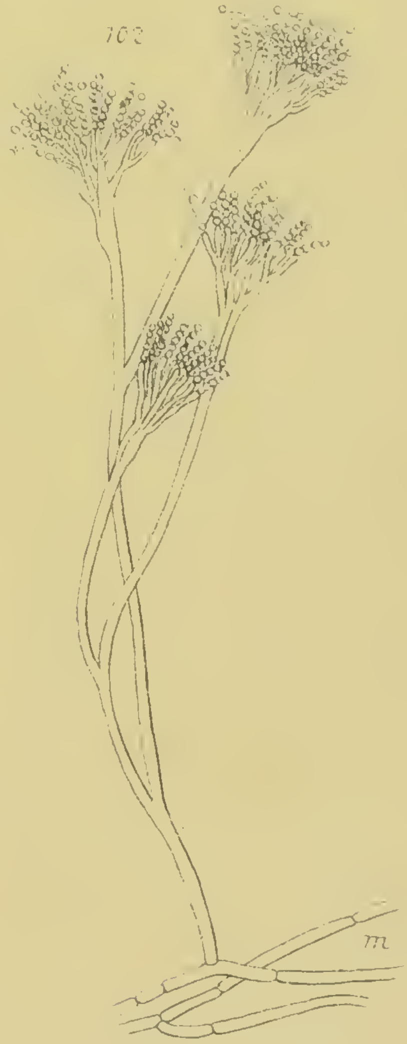

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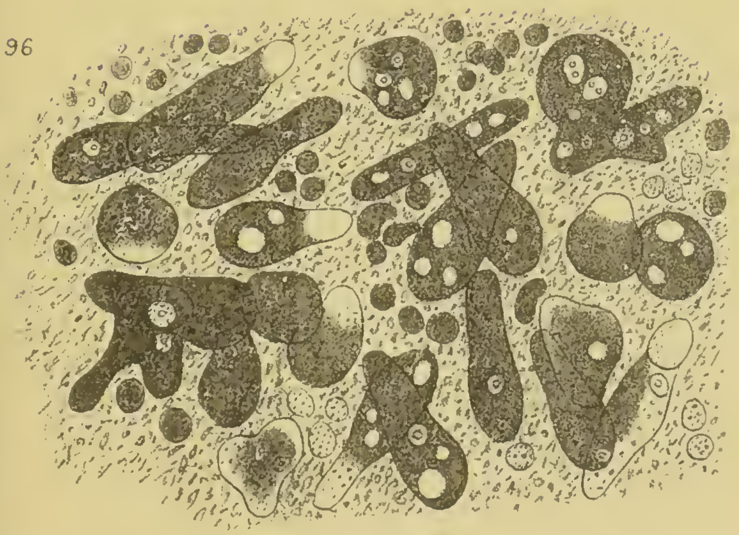

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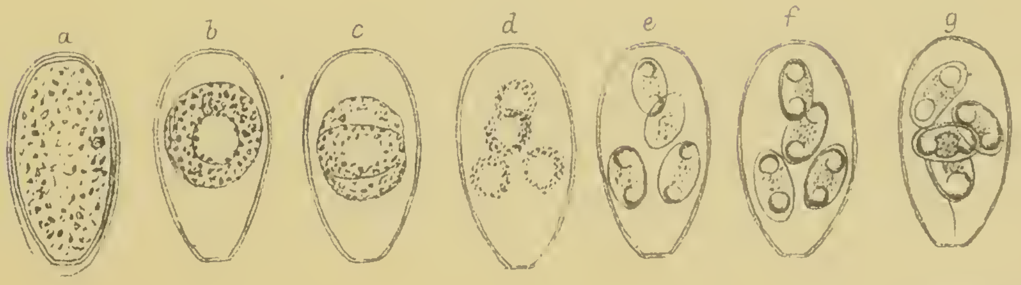

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PLATE XLII

This plate is copied from Golgi, Studien über Malaria, 'Fortschritte der Medicin,' Bd. IV, Tafel III.

Figs.

108–119 show the malaria plasmodium as a pale amœboid body inside a red blood disc. It gradually increases in size at the expense of the substance of the red blood disc: in 116–119 it has become conspicuously enlarged, and contains masses of pigment granules derived from the hæmoglobin.

120–125 show the various progressive stages in the process of the cleavage of the plasmodium and the gradual shifting of the pigment granules.

126–131 show the completion of the process of cleavage and the final isolation of the spores; the dark granules are the pigment granules.

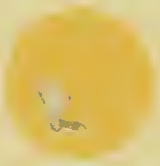
132–138 are oval parasites—Laveran's corpuscles, from atypical cases of malaria.

108

109

110

111



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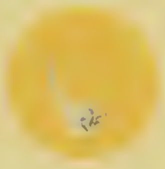

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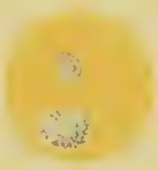

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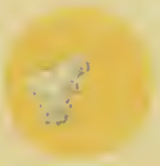

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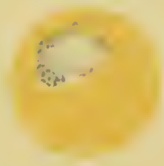

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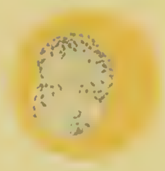

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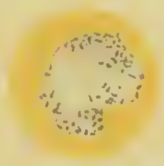

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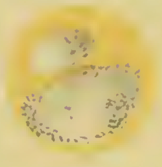

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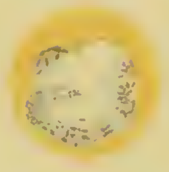

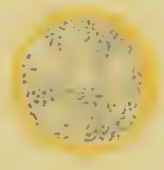

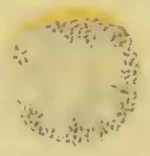

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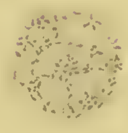

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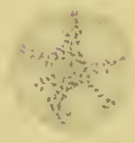

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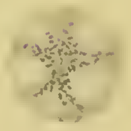

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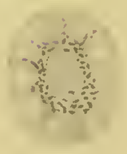

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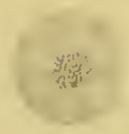

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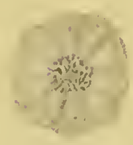

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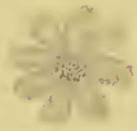

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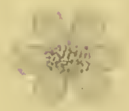

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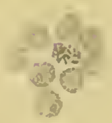

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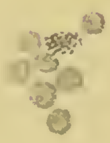

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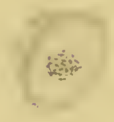

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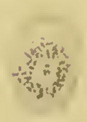

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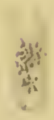

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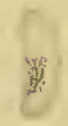

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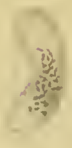

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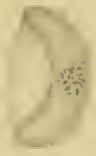

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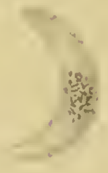

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